ELI LILLY AND COMPANY, Plaintiff, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, and INTERNEURON PHARMACEUTICALS, INC., Involuntary Plaintiffs, vs. TEVA PHARMACEUTICALS USA, INC., Defendant.

IP 02-0512-C-B/S

UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF INDIANA, INDIANAPOLIS DIVISION

2004 U.S. Dist. LEXIS 14724

July 29, 2004, Decided

PRIOR HISTORY: **Eli Lilly & Co. v. Teva Pharms. USA, Inc., 2003 U.S. Dist. LEXIS 13069 (S.D. Ind., July 21, 2003)**

DISPOSITION: Patent was found valid and enforceable.

COUNSEL: [*1] For Eli Lilly and Company, PLAINTIFF: Donald Knebel, Barnes & Thornburg, Indianapolis, IN USA. Dominick A Conde, Fitzpatrick Cella Harper & Scinto, New York, NY USA.

For Massachusetts Instit of Tech, PLAINTIFF: Donald Knebel, Barnes & Thornburg, Indianapolis, IN USA. Jeffrey C McDermott, Krieg Devault Alexander Capehart, Indianapolis, IN USA. Timothy J Vezeau, Katten Muchin Zavis Rosenman, Chicago, IL USA.

For Interneuron Pharmaceuticals Inc, PLAINTIFF: Donald Knebel, Barnes & Thornburg, Indianapolis, IN USA. Jeffrey C McDermott, Krieg Devault Alexander Capehart, Indianapolis, IN USA. Timothy J Vezeau, Katten Muchin Zavis Rosenman, Chicago, IL USA. Brian H Corcoran, Katten Muchin Zavis Rosenman, Washington, DC USA.

For Teva Pharmaceuticals USA Inc, DEFENDANT: David O Tittle, Bingham McHale, LLP, Indianapolis, IN USA. Steven J Lee, Kenyon & Kenyon, New York, NY USA.

JUDGES: SARAH EVANS BARKER, JUDGE, United States District Judge.

OPINIONBY: SARAH EVANS BARKER

OPINION: FINDINGS OF FACT AND CONCLUSIONS OF LAW

This case comes before the court, after a bench trial held November 12-24, 2003, for decision on the issue of patent invalidity under **35 U.S.C. §§ 102** [*2] and **103**. Plaintiff, Eli Lilly and Company ("Lilly"), filed suit against Defendant, Teva Pharmaceuticals USA, Inc. ("Teva"), for infringement of **U.S. Patent No. 4,971,998** ("the '998 patent"). Teva conceded, based on the court's July 21, 2003 Claim Construction ruling, that its generic drug indication infringed Claim 2 of the '998 patent. Therefore, the only decision currently before the court is whether the '998 patent is invalid, either as anticipated under **35 U.S.C. § 102** or obvious under **35 U.S.C. § 103**. For the reasons explicated below, we conclude that the '998 patent was neither anticipated nor obvious, and is, therefore, valid and enforceable.

Findings of Fact

I. Background n1

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n1 Unless otherwise indicated, these background facts are taken from the parties' joint submission of Facts That Are Admitted and Will Require No Proof at Trial. (Dkt. # 167.)

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Plaintiff Eli Lilly and Company ("Lilly") is a corporation organized and existing under [*3] the laws of the State of Indiana, having its principal place of business in Indianapolis, Indiana. Lilly is engaged in the business of research, development, and commercialization of pharmaceutical drugs. (See Tollefson Tr. p. 883). Involuntary plaintiff Massachusetts Institute of Technology ("MIT") is a university located in Cambridge, Massachusetts. Involuntary plaintiff Interneuron Pharmaceuticals, Inc. ("Interneuron") is a Delaware corporation having its principal place of business in Lexington, Massachusetts. Interneuron is now known as Indevus Pharmaceuticals, Inc. Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation organized and existing under the laws of the State of Delaware, having its administrative offices in North Wales, Pennsylvania, and a principal place of business in Selleville, Pennsylvania. Teva is engaged in the generic manufacture of pharmaceutical drugs.

This patent infringement action arises under **35 U.S.C. §§ 271(e)** and **281-283**. Subject matter jurisdiction is proper under **28 U.S.C. §§ 1331** and **1338(a)**. Venue is proper under **28 U.S.C. §§ 1391(c)** and **1400(b)**.

II. [*4] **Trial Witnesses**

A. Lilly's trial witnesses:. Dr. Richard Wurtman, a co-inventor of the '998 patent, is the Cecil H. Green Distinguished Professor in the Department of Brain and Cognitive Science at MIT. (R. Wurtman Tr. pp. 6-7, 11). He holds an M.D. from Harvard University and also trained at the National Institutes of Health. (R. Wurtman Tr. p. 7). Dr. Wurtman has published about 1000 articles relating to his research, which focuses on neurotransmitters and their effect on the brain and behavior. (R. Wurtman Tr. p. 12).

. Dr. Judith Wurtman, the other co-inventor of the '998 patent, directs a program in women's studies at the Clinical Research Center at MIT, and is also the founder and director of a private weight loss center in the Boston area. (J. Wurtman Tr. p. 157). She holds a Ph.D. in cell biology from George Washington University, and also did post-doctoral work in nutritional biochemistry at MIT. (J. Wurtman Tr. pp. 158-59).

. Dr. Gary Tollefson is Vice-President of Lilly's Research Laboratories, and holds an undergraduate degree in Psychology, an M.D., and a Ph.D. in Psychopharmacology, all from the University of Minnesota. (Tollefson [*5] Tr. p. 880). Dr. Tollefson was previously Chairman of the Department of Psychiatry at St. Paul Ramsey Medical Center, and Associate Professor, Department of Psychiatry, University of Minnesota. (Tollefson Tr. p. 881). He joined Lilly in 1991, and later held the position of fluoxetine team leader, responsible for the development of Sarafem(R). (Tollefson Tr. pp. 881-82).

. Dr. Jean Endicott is Professor of Clinical Psychology at the College of Physicians and

Surgeons, Columbia University, Department of Psychiatry, and the Director of the Premenstrual Evaluation Unit at Columbia Presbyterian Medical Center. Dr. Endicott is also the Chief of the Department of Research Assessment and Training at the New York State Psychiatric Institute. (Endicott Tr. p. 1043). Dr. Endicott has a Ph.D. in Clinical Psychology from Columbia University, but is not a medical doctor. (PTX 5, Ex. A.) Dr. Endicott has authored, or co-authored, more than fifty publications regarding PMS (Endicott Tr. pp. 1045-46), and has more than twenty years of experience in the treatment of women suffering from PMS, including designing and executing clinical trials since 1982. (Endicott Tr. pp. 1043-44). Dr. Endicott [*6] has served on the Editorial Board of the numerous publications. (Endicott Tr. pp. 1046-47). She has also been a consultant and member of several prestigious professional committees including the Task Force on Nomenclature and Statistics of the American Psychiatric Association for DSM-III and DSM-III-R, which was responsible for deriving the definition of Late Luteal Phase Dysphoric Disorder ("LLPDD") in 1987. (Endicott Tr. p. 1045). As well, she was a member of the "LLPDD/PMDD" Work Group DSM-IV which in 1994 derived the definition of PMDD. (Endicott Tr. pp. 1045-46).

. Dr. Lynda Smirz is an Obstetrician/Gynecologist in private practice at the Women's Health Alliance in Indianapolis, Indiana. (Smirz Tr. p. 1296). She has over 20 years of experience in obstetrics and gynecology. (Smirz Tr. p. 1296-97). Dr. Smirz also served as a Clinical Assistant Professor, Department of Obstetrics and Gynecology, Indiana University School of Medicine. (Smirz Tr. p. 1297). Dr. Smirz sees patients regularly and is familiar with the key scientific literature relating to the standard of care among Obstetricians and Gynecologists for the treatment of PMS as of October 1987. (Smirz Tr. pp. 1298-1300). [*7]

. Dr. Pierre Blier is Professor, Departments of Psychiatry and Neuroscience at the University of Florida. (Blier Tr. p. 1348). Dr. Blier began his research on serotonin in 1978. (Blier Tr. p. 1349). He holds a Master's and a Ph.D. in Neuroscience, and an M.D., all from the Universite de Montreal. Dr. Blier also completed a post-doctoral fellowship in the neuropharmacology of serotonin at Laboratoires d'Etude et de Recherche Synthelabo in Paris. Dr. Blier currently serves on the numerous Editorial Boards and is an Editor for the *Journal of Psychiatry* and *Neuroscience*. (Blier Tr. p. 1350). Dr. Blier has authored or co-authored 170 peer-reviewed publications; he also consults extensively with pharmaceutical firms. (Blier Tr. p. 1349).

. Dr. Daniel Smith is the Clare W. Barker Chair and Professor of Marketing, and Associate Dean of Academics at the Kelley School of Business, Indiana University, Bloomington, Indiana. (Smith Tr. p. 942). Dr. Smith has over 15 years of experience in Marketing, with an emphasis on brand and product line management. (Smith 942:25-943:9).

. Mr. Michael Tate is Managing Director of InteCap, Inc., an international business consulting [*8] firm that focuses on intellectual property matters in the context of litigation, valuation and licensing. (Tate 1211:9-17). Mr. Tate has over 15 years of experience in business consulting, which has included serving as a consultant and expert witness in a wide range of litigation matters. These matters involved analysis and evaluation of financial and accounting data for the purpose of determining the extent of economic damages as well as the valuation of various intellectual property rights and the determination of reasonable royalty rates. (Tate Tr. pp. 1211-12).

B. Teva's trial witnesses:. Dr. Laura Miller is Associate Head of the Department of Psychiatry, Chief of the UIC Women's Mental Health Program, and an Associate Professor of Psychiatry at University of Illinois at Chicago ("UIC"). Her responsibilities include designing and implementing clinical and teaching programs related to women's mental health. (DTX VN, ZE; Miller Tr. p. 204.) Dr. Miller has never, however, been involved with a clinical trial

relating to PMS. (Miller Tr. p. 373.) Dr. Miller graduated from Harvard Medical School in 1982 and completed her psychiatry residency at the University of Chicago [*9] from 1983-86. (DTX VN, ZE.) Though, as of October 1987, Dr. Miller was not board certified (DTX ZE) and had not prescribed any agents to women suffering from LLPDD (Miller 375:12-19), she has since become a board-certified psychiatrist and developed particular expertise in the treatment of women's reproductive-related mental illness, including premenstrual mood disturbances. (DTX VN, ZE; Miller Tr. pp. 204-5.) The use of fenfluramine, which is not a psychotropic drug, to treat eating disorders is outside her area of expertise. (Miller Tr. pp. 502-03). She has authored or co-authored numerous articles, given talks or discussions at university or professional forums and taught graduate level and continuing medical education classes related to psychiatric conditions in women, including those related to the menstrual cycle. (DTX ZE.) She published her first article on PMS in 2000. (Miller Tr. pp. 372-73). In addition, Dr. Miller was asked by both the American Psychiatric Association and Continuing Medical Education Incorporated to write their review articles on premenstrual mood disorders. (DTX ZE.)

. Dr. Andrea Rapkin is a Professor in the Department of Obstetrics and Gynecology [*10] ("OB/GYN") of the UCLA Medical Center. (DTX VO; Rapkin Tr. p. 541-42.) Dr. Rapkin graduated from medical school in 1979, and finished her OB/GYN residency in 1983. (Id.) Dr. Rapkin has been a principal investigator on approximately thirty clinical studies and has published over thirty research papers. She is a reviewer for the major OB/GYN journals. (Rapkin Tr. pp. 542-43.) Dr. Rapkin is also the lead author of the prior art reference entitled "Whole Blood Serotonin in Premenstrual Syndrome," which was published in the journal "Obstetrics and Gynecology." (DTX FF; Rapkin Tr. p. 544.)

. Dr. Walter Brown is a Clinical Professor of Psychiatry at the Brown University School of Medicine and at the Tufts University School of Medicine. Dr. Brown has been on the faculty at Brown University since 1974. Prior to joining the faculty of Brown University, he held academic appointments at the Mount Sinai School of Medicine in New York and at the Yale University School of Medicine in Connecticut. (DTX VL, ZG; Brown Tr. p. 651.) Dr. Brown received an M.D. from Duke University in 1967, and completed his residency at the Yale University Department of Psychiatry from July 1968 through June [*11] 1969, and from July 1971 through June 1972. He held fellowship positions at the National Institute of Child Health and Human Development/National Institutes of Health in Bethesda, Maryland, from July 1969 through June 1971, and at Yale University from July 1972 through June 1974. (DTX VL, ZG.) Dr. Brown has been a practicing psychiatrist and has conducted clinical research in the area of psychiatry for about thirty years. (Brown Tr. p. 651.) Dr. Brown has been a principal investigator in over 100 clinical trials, including trials relating to the drug fluoxetine. (DTX VL, ZG; Brown Tr. pp. 651, 653.) Dr. Brown has co-authored several articles relating to the use of fluoxetine in the treatment of PMS, the first in 1990. (DTX VL, ZG, GJ; Brown Tr. p. 651; 653-54.)

. Dr. Sanford Bolton is an expert in biostatistics. (DTX VK, ZF; Bolton Tr. p. 833.) He received his Ph.D. in Pharmacy from the University of Wisconsin in 1958, and his Masters in Biostatistics from Columbia University in 1966. (Id.) Over his forty-year career in biostatistics, he has published numerous articles in the field and is the author of the treatise entitled "Statistics in Clinical Studies and Pharmaceutical [*12] Processes." (Id.)

. Mr. George Gould is an expert in pharmaceutical licensing. (DTX VM, XR; Gould Tr. p. 1001.) He received a B.A. in Organic Chemistry in 1958 from Johns Hopkins University, a J.D. in 1963 from Columbia University School of Law, and a LL.M. in 1973 from New York University Law School. (DTX VM, XR.) Mr. Gould has over thirty years of licensing experience in the pharmaceutical industry. Among other things, Mr. Gould was vice-

president of licensing and corporate development and chief patent counsel at an international pharmaceutical company, Hoffmann-La Roche Inc. (DTX VM, XR; Gould Tr. p. 1002-3.) Over the course of his career, Mr. Gould has negotiated several hundred licenses in the pharmaceutical field for large pharmaceutical as well as start-up biotech companies. (Id.)

. Dr. David Schmittlein is a marketing expert. He is currently the Ira A. Lipman Professor, Professor of Marketing and the Deputy Dean and Chief Academic Officer of the Wharton School of the University of Pennsylvania. His twenty-three years at the Wharton School have been spent teaching, consulting and conducting research in the field of marketing. (DTX VP, YE; Schmittlein [*13] pp. 1247-48.) Dr. Schmittlein received a bachelor's degree in Mathematics from Brown University and a Ph.D. in Business from Columbia University in 1980. (DTX VP, YE; Schmittlein Tr. p. 1248.) Dr. Schmittlein has authored over forty research publications, which have been published in the major journals in marketing, statistics and economics. (DTX VP, YE; Schmittlein Tr. p. 1249.)**III. Prozac(R) n2--Lilly's Development of Fluoxetine**

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n2 We respect that Prozac, like the other pharmaceutical brand names used in this Entry, is a registered trademark. Therefore, we acknowledge the trademark upon our first use of each brand name. Thereafter, however, so as not to add to an already detailed Entry, we omit the trademark symbols.

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Fluoxetine belongs to a class of compounds called selective serotonin reuptake inhibitors ("SSRIs"). (Dkt. # 167). During the 1970s and 1980s, Lilly researched, developed and tested the drug fluoxetine. (See, e.g., DTX A, WY). In 1977, Lilly was issued **U.S. Patent No. 4,018,895** [*14] ("the '895 patent") entitled "Aryloxyphenylpropylamines in Treating Depression." (DTX A cover page.) The '895 patent claimed a method of treating humans suffering from depression with a daily dosage of 1 to 200 mg of fluoxetine. (DTX A, col. 18, l. 1-2; col. 17, l. 28-30.) The '895 patent also mentions the usefulness of fluoxetine in treating disorders of sleep, sexual performance, appetite, muscular function and pituitary function; however, it does not mention PMS or the treatment thereof. (Miller Tr. pp. 437-38; DTX A col. 14, ll. 17-22; Endicott Tr. pp. 1059-60).

Then, in 1986, Lilly was issued **U.S. Patent No. 4,590,213** ("the 213 patent") entitled "Anti-Anxiety Method." (DTX WY cover page). The '213 patent claims a method for treating anxiety in humans, both men and women, in need of such treatment with the daily administration of 20-80 mg of fluoxetine. (DTX WY col. 1, l. 52-56; col. 2. 34-35.) Although the '213 patent adds schizophrenia and hypothermia to the list of disorders treatable with fluoxetine in the '895 patent, the '213 patent, like the '895 patent, does not mention PMS. (Miller Tr. pp. 437-39; Endicott Tr. pp. 1061-63).

As part of the research and development of [*15] fluoxetine, Lilly conducted numerous clinical trials, which established the efficacy of fluoxetine in the treatment of major depressive disorder. In March 1985, Paul Stark, the inventor of the '213 patent, and C. David Hardison, a Lilly employee, published a study, *A Review of Multicenter Controlled Studies of Fluoxetine vs. Imipramine and Placebo in Outpatients with Major Depressive Disorder,* 46 J. Clin. Psychiatry 53-58 (1985) (the "Stark reference"), which determined that fluoxetine relieved the symptoms of depression equally as well as another antidepressant,

impramine, and significantly better than placebo, with fewer and less severe side effects than impramine. (DTX GB pp. 53, 57)

Stark intended to test a hypothesis that a deficiency of serotonin caused affective disorders, including depression. He stated, "According to one serotonin hypothesis of depression, reduced serotonin function is manifested in depressive symptoms. Thus, a compound [like fluoxetine] that selectively inhibits the reuptake of serotonin, enhancing serotonin function, should ameliorate the symptoms of depression." (Id. p. 53.) Among Stark's patients were men and women. Some of these women likely [*16] would have been premenopausal; however, Stark did not diagnose any of them with PMS. Such a diagnosis was not necessary given the purpose of Stark's study, which was to treat depression, not PMS. Although Stark spoke of treating the symptoms of depression, he never suggested the use of fluoxetine to treat PMS. (See Miller Tr. pp. 433-34).

Also in March 1985, J.B. Cohn and Charles Wilcox published a study comparing the efficacy and safety of fluoxetine with those of imipramine and placebo. *A Comparison of Fluoxetine, Imipramine, and Placebo in Patients with Major Depressive Disorder,* 46 J. Clin. Psychiatry 26-31 (1985) (the "Cohn reference"). Like Stark, Cohn posited that "fluoxetine's specific inhibition of serotonin reuptake by the neuron suggest that this compound might be an effective antidepressant." Again, Cohn found that "fluoxetine relieved the symptoms of depression better than placebo and with fewer and less severe side effects ... than imipramine." (DTX AV pp. 28-29, 31.) Cohn, too, treated outpatients with major depressive illness, a class that presumably would have included both men and women of varying ages. He did not diagnose any of the women with PMS or even [*17] mention PMS, thereby demonstrating that he had no intent to treat the syndrome. (See Miller Tr. pp. 435-36).

The PTO examiner did not consider either the Stark reference or the Cohn reference during the prosecution of the applications that led to the issuance of the '998 patent. (DTX K, M, N.) However, the Stark and Cohn references lend further support to the claims of the '895 and '213 patents. They neither teach away from the patented inventions nor extend the serotonin hypothesis to PMS.

In addition to clinical trials like those conducted by Stark and Cohn, Lilly conducted large-scale clinical trials of fluoxetine in order to gain FDA approval to market the drug ("Fluoxetine Trials"). (Dk. # 167, P19; see also Bolton Tr. p. 836.) The records of these clinical trials were confidential, and as such, were not known to anyone outside of Lilly, including the Wurtmans or the examiner of the '998 patent. Lilly and the clinical investigators conducting the trials were required to maintain the confidentiality of these records. (DTX MW at P 104 3236)

A number of the pre-October 1986 Fluoxetine Trials had an "open label" arm where both the patient and the physician knew whether [*18] the patient was being treated with fluoxetine. (DTX AV at 26, MP, Brown Tr. p. 653.) During these open-label trials, fluoxetine was administered to, among others, at least 112 women between the ages of 18 and 45 who were diagnosed with major depressive disorder. This diagnosis did not include PMS specifically as these trials were not intended to test the efficacy of fluoxetine as a PMS therapy. PMS requires a careful diagnosis, which must be charted over several menstrual cycles in order to avoid the retrospective misallocation of mood changes to the menstrual cycle. (See Rapkin Tr. pp. 593, 596-97; Brown Tr. pp. 783-84, 787; Bolton Tr. 864-65; Endicott Tr. pp. 1063, 1066; PTX 206 at 1539; PTX 205 at 46; DTX FR p. 390). These 112 women with major depressive disorder were administered fluoxetine in daily dosages between 5 mg to 120 mg over a period of at least thirty days. (D-DEM O; DTX XC; Bolton Tr. p. 843.)

As part of Teva's anticipation claim, Teva engaged Dr. Bolton, a statistical expert, to calculate the probability that one or more of these 112 women with major depressive disorder also had disturbances of mood, disturbance of appetite, or both associated with PMS. Dr. Bolton [*19] used the binomial equation to calculate the probability of a specific event occurring where there are two possible outcomes, *i.e.,* the woman has a disturbance of mood and/or appetite associated with PMS or does not have such a disturbance. (Bolton Tr. pp. 845-46; D-DEM P.) In performing his calculations, Dr. Bolton assumed the prevalence rate of premenstrual depression among these women to be 65 percent, a rate taken from the expert report of Dr. Miller. n3 (Bolton Tr. p. 851; 865-66.) With this prevalence rate, Dr. Bolton calculated the probability that one or more of the 112 women with major depressive disorder also had disturbances of mood, disturbance of appetite, or both associated with PMS to be greater than 99.99999 percent. (Bolton 852:7-852:16; D-DEM W). Lilly challenges the 65 percent prevalence rate used by Dr. Bolton because it measures a lifetime, not a concurrent, possibility that the two disorders will co-occur. (DTX FR at 390.) Dr. Bolton, however, responded that even if the prevalence rate of premenstrual depression among women who suffer from depressive disorders was as low as 10 percent, the probability that at least one of the 112 women had PMS would be 99.99925 [*20] percent. (Bolton Tr. pp. 853-54; D-DEM Y.)

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n3 Dr. Miller testified that the prevalence rate of premenstrual depression among women who suffer from depressive disorders has been estimated in several studies to be approximately 65 percent. (See, e.g., DTX FR (June 1987) at 390; Miller Tr. pp. 232-33.)

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Dr. Bolton, of course, speaks in probabilities. He could not identify any one patient record and say with certainty that a female subject actually had PMS. (Bolton Tr. p. 871). Moreover, as stated above, none of the clinical trial participants, which included both men and women, were actually diagnosed with PMS. They were not diagnosed with PMS because in that context it was irrelevant; the purpose of the Prozac clinical trials was to determine the effectiveness of fluoxetine in treating depression, not PMS. (Brown Tr. pp. 783-84; Bolton Tr. pp. 864-65, 868-69; Endicott Tr. pp. 1063-65). To address this criticism of Dr. Bolton's analysis, Teva asked another of its experts, Dr. Brown, to examine the patient record [*21] for one of the 112 women in Dr. Bolton's sample. A patient record is a document used by clinical researchers to record all of the information gathered on a single research subject during a clinical trial. (Brown Tr. p. 686). The patient record was of a 37-year old woman with major depressive disorder ("the patient") who participated in a fluoxetine clinical trial in 1982. (DTX LD; Brown Tr. pp. 688-89.) At the beginning of the trial, the patient was asked from what other illnesses or conditions did she suffer. She indicated that she had hay fever, but did not mention PMS. (Endicott Tr. pp. 1064-65; DTX LD at P 58 730). In the normal course, however, Dr. Endicott testified that, if the patient suffered from PMS, she would have mentioned it. (Endicott Tr. pp. 1141-43, 1143-45).

The patient was in the double-blind portion of the study for the first eight weeks. (See Brown Tr. p. 709; DTX LD at PZ 58 727-PZ 58 800.) The patient began the open-label phase of the study one month after the completion of the double-blind study. The open-label phase lasted for six to seven months. The patient record indicated that for most of the open-label phase the patient was given 60 mg of fluoxetine [*22] daily, while at the end of the open-label phase, the daily dosage of fluoxetine was 20 mg. (Brown Tr. pp. 709-11,

726.)

The patient record for week 5 stated that the patient experienced "premenstrual tension," which the patient record explains as "premenstrual problems of tension and irritability." The patient also reported that she "felt worse last week. She said she always feels more depressed [and] tense before her menstrual periods." (Brown Tr. pp. 704-05; DTX LD at PZ 58 768, PZ 58 772.) At the patient's next visit, which was week 6, she reported that "premenstrual tension [was] very much less last week than usually experienced." (DTX LD at PZ 58 780; Brown Tr. pp. 705-06.) The patient record also contains results of the Hamilton Psychiatric Rating Scale for Depression, which measures the severity of depression. (Brown Tr. p. 689.) The patient's Hamilton Depression Rating decreased from 12 in week 5 to 7 in week 6. Dr. Brown testified that this decrease is consistent with the patient having experienced premenstrual tension during week 5 which was relieved by week 6. (Brown Tr. p. 706.)

In spite of the anecdotal comments in the patient record relied on by Dr. Brown, the patient [*23] record simply does not supply sufficient information to make a PMS diagnosis. (Endicott Tr. pp. 1065-66). For example, as Dr. Brown did not (and could not have) interviewed the patient, we have no information concerning the date of the onset of menses; similarly, we do not have any evidence of daily ratings or documentation that she had the PMS before she was diagnosed with major depression. (Id. pp. 1145-46; see also Brown Tr. p. 785). Many women attribute the occurrence of their symptoms to the menstrual cycle, but when carefully examined, those women do not actually have PMS. (Endicott Tr. p. 1066). Dr. Brown conceded that "when thoroughly evaluated, the overwhelming majority of women who say they have PMS do not in fact have disabling symptoms related specifically to the menstrual cycle." (Brown Tr. p. 787; PTX 211 at 570).

An accurate diagnosis of PMS requires daily prospective ratings, taken over two months, in order to show whether symptoms onset during the luteal phase and remit during the follicular phase, which is the hallmark of PMS. (Rapkin Tr. pp. 593, 596-97; Endicott Tr. p. 1066; PTX 206 p. 1539; PTX 205 at 46). Dr. Miller admitted that charting is the most [*24] accurate, but not the only, way to diagnose PMS, and Dr. Brown stated that the "acid test for PMS is prospective ratings." (Miller Tr. p. 383, 386; Brown Tr. p. 787; PTX 199 p. 55; PTX 211 p. 570). Two months of ratings are used in order to rule out the possibility that in any one month the symptoms could have been caused by some other issue such as problems at work, unpaid bills, or other life stresses. (Rapkin Tr. p. 597; Endicott Tr. p. 1066). Dr. Brown admitted that there were no reports of PMS rating scales in the patient record he reviewed. (Brown Tr. p. 788). Thus, in the absence of daily ratings, a patient's self report is insufficient to make an accurate diagnosis of PMS. (Endicott Tr. p. 1066).

Relying only on a patient's recollection can lead to misdiagnosis, especially when the patient suffers from PMS and major depressive disorder. (Rapkin Tr. 593-96; Endicott Tr. p. 1066, 1145-46, PTX 205 p. 46). Dr. Endicott testified that it is very difficult to diagnose PMS in a woman who has major depressive disorder. (Endicott Tr. pp. 1066-67). They share symptoms, and one needs to carefully examine the patient to ensure that the symptoms onset during the luteal phase and offset [*25] during the follicular phase. (Id. p. 1067).

All of the 112 patients in Dr. Bolton's sample were taking fluoxetine during the open label phase of the clinical trial. The evidence is less clear as to whether the patient was taking fluoxetine during the blinded portion, during which she complained of premenstrual tension. Lilly never produced the protocol for this study. Lilly did, however, release protocols for other clinical trials. Those protocols indicate that a patient could not receive fluoxetine

during the open-label phase of a clinical trial unless the patient had received fluoxetine during the double-blind phase and had substantially improved during the double-blind phase and exhibited a clinically significant response, or that patient had received a drug other than fluoxetine and not exhibited a clinically significant response. (DTX NB at PZ 6 1560, MZ at PZ 6 2260, MU at PZ 918 1121, MP at PZ 6 1566, MY at PZ 6 1557.)

Because this individual patient was on fluoxetine in the open-label portion and had substantially improved during the double-blind phase, we conclude that she was on fluoxetine during the double-blind portion. (See Brown Tr. pp. 722-23.) This reasoning [*26] is supported by her Hamilton Depression Ratings, which substantially improved over four weeks, a result consistent with the patient taking fluoxetine. (See Brown Tr. p. 703.) In addition, the patient lost weight, which was also consistent with fluoxetine effects. (Brown Tr. pp. 689, 705-06, 707-08, 711; Miller Tr. p. 263). However, one inconsistency: if the patient was being treated with fluoxetine at the time of her comment, then one would expect (based on what we now know) that given the rapid action of fluoxetine in relieving PMS symptoms, she would not have any PMS symptoms in Week 5 because she would have been administered fluoxetine for at least one week prior to her comments. (Endicott Tr. pp. 1068-69, 1146-47). Therefore, we conclude that the patient, while likely given fluoxetine to treat her major depression, did not have PMS.

The patent examiner did not consider the Fluoxetine Trials during prosecution of the applications that led to the issuance of the '998 patent. (DTX M, N.) In an August 4, 1988 office action during prosecution of U.S. Patent Application Ser. No. 111,771, the first application in the series from which the '998 patent issued, the patent examiner rejected [*27] the pending claims, which included methods of treatment using the drug d-fenfluramine. One of the bases of the patent examiner's rejection was that the prior use of d-fenfluramine in clinical work would have inherently anticipated the pending claims:All of the clinical work with [d-fenfluramine] has clearly involved treating a large number of women of menstruating age with this compound. Given the common occurrence of PMS among such women the claimed method would have to inherently haven't [sic] been practiced in one or more of the patients used in the study. In addition, if this drug is now a commonly prescribed drug this would provide further evidence that it would have inherently (if unintentionally) been used in carrying out claimed process.(DTX M at 137, Office Action, U.S. App. Ser. 07/111,771, dated Aug. 4, 1988 at 5.) In the same office action, the patent examiner requested more information from the Wurtmans and MIT: "In evaluating the merits of the above prior art rejection it would be helpful to know approximately what percentage of menstruating women regularly experience PMS. If applicants have knowledge on this question they are requested to make it [*28] of record with their response to this office action." (DTX M at 138, Office Action, U.S. App. Ser. 07/111,771, dated Aug. 4, 1988 at 6.)

First, we disagree with the patent examiner that the Fluoxetine Trials would have been relevant. Not only did they not demonstrate an intent to treat PMS, but as shown above, without a specific diagnosis of PMS, it would have been impossible to tell whether the claimed method had been inherently practiced. In addition, although some studies indicate that the prevalence rate of PMS among women with major depression is approximately 65 percent, as shown above, that number reflects a lifetime, not concurrent, prevalence rate. Most importantly, assuming *arguendo* that these records would have been relevant, the Wurtmans would not have had access to these Fluoxetine Trial records at the time of the filing of the '998 patent. The clinical records were the confidential property of Lilly. (DTX MW p. P 104 3236).

On September 6, 1983, Lilly filed a New Drug Application ("NDA"), No. 18-936, with the

FDA, seeking approval to market fluoxetine for major depressive disorder. The FDA approved Lilly's NDA on December 29, 1987. Lilly was the exclusive marketer [*29] of fluoxetine in the U.S. from January 1988, when Prozac came on the market, through August 2001, when the Federal Circuit declared invalid the last of Lilly's fluoxetine-related patents. (Dkt. # 167, **Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955 (Fed. Cir. 2001)**.) Prozac was one of the best-selling drugs in the world, having achieved over a billion dollars in sales. (See Smith Tr. p. 984.)

IV. The '998 patent

In the mid-to-late 1970's, the Wurtmans, inventors of the '998 patent, developed a theory that the food individuals consume affects brain serotonin. (R. Wurtman Tr. pp. 17-18). To test this theory scientifically, they conducted animal studies to determine if the administration of drugs known to increase serotonin, in particular fenfluramine and fluoxetine, would cause a reduction in carbohydrate consumption. (Id. pp. 18-19.). From these studies, they concluded that fenfluramine and fluoxetine caused the animals to eat less carbohydrate in proportion to protein, and also to consume fewer calories. (R. Wurtman Tr. pp. 19-20; J. Wurtman Tr. pp. 159-60). In about 1977, they published this research. (DTX HA at 1179; PTX 133 at 902).

The [*30] Wurtmans then applied their theory to humans who complained of craving carbohydrates. (R. Wurtman Tr. pp. 21-22). Those patients were referred to as having "Carbohydrate Craving Obesity" ("CCO"), a term coined by Dr. Judith Wurtman. (R. Wurtman Tr. p. 22; J. Wurtman Tr p. 161). After directly measuring the food intake of these subjects to determine whether they actually overconsumed carbohydrates, the Wurtmans determined that these patients had a specific appetite for carbohydrates, which occurred at a particular time of day, resulting in an overconsumption of calories and weight gain. (R. Wurtman Tr. pp. 22-24; J. Wurtman 160-61; PTX 132 p. 215-16). Based on this data, the Wurtmans conducted a clinical trial in which they tested whether overconsumption could be suppressed by fenfluramine, which increases brain serotonin release. (R. Wurtman Tr. pp. 22-23; J. Wurtman Tr. pp. 161-62; PTX 132 p. 215-16). In 1983, they first published the results of that clinical study, which showed that fenfluramine suppresses carbohydrate intake. (R. Wurtman Tr. pp. 22-24; J. Wurtman Tr. p. 162; PTX 132 p. 215-16).

Also in the early 1980s, the Wurtmans were issued two patents resulting from their work [*31] on CCO, **U.S. Patent No. 4,309,445** ("the '445 patent") entitled "D-Fenfluramine for Modifying Feeding Behavior," and 4,452,815 ("the '815 patent") entitled "Method of Utilizing D,L-Fenfluramine for Modifying Feeding Behavior." (DTX WW (1982), WX (1984)). The '815 patent teaches the Wurtmans' discovery that carbohydrate cravings "tend to occur at characteristic times of the day and are often enhanced by stress or, in women, by premenstrual tension." (DTX WX col. 1, ll. 26-28). The '815 patent also states that patients to be treated with d,l-fenfluramine are characterized by, among other things, "an appetite occurring according to a regular circadian cycle, and the resulting circadian maxima can be in relation to the menstruation cycle." (DTX WW col. 3, ll. 1-3.) Although the Wurtmans suggest in passing that carbohydrate craving could be associated with the menstrual cycle, CCO is not limited to women. In addition, the '815 patent disclosed that the described activity of d,l-fenfluramine "appears to be mediated by the serotoninergic system." (DTX WW at col. 3, ll. 34-35.) Due at least in part to the Wurtmans' research, it was well-known by 1987 that serotonin regulated carbohydrate intake. [*32] (DTX XI (1987)).

In the early 1980s, however, the Wurtmans' theory regarding the relationship between carbohydrate intake and serotonin was not widely accepted by the scientific community. The

conventional wisdom was that overweight people overconsumed carbohydrates simply out of habit. (R. Wurtman Tr. pp. 24-25; J. Wurtman Tr. p. 162). To respond to this criticism, the Wurtmans decided to test patient groups whose carbohydrate craving was not habitual. They identified three potential groups: (1) those with Seasonal Affective Disorder ("SAD"), who overconsumed carbohydrates only in the winter months; (2) those who suffered from premenstrual syndrome ("PMS"), n4 who were thought to overconsume sweet or salty carbohydrates during the luteal phase of the menstrual cycle; and (3) those who had nicotine withdrawal after they stopped smoking. (R. Wurtman Tr. pp. 25-26; J. Wurtman Tr. pp. 162-64).

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n4 As used herein, the term "PMS" includes LLPDD/PMDD, in accordance with the Court's claim construction. Additionally, LLPDD and PMDD are used herein interchangeably. (Rapkin Tr. p. 601).

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To test their theory, the Wurtmans scientifically measured whether SAD subjects overconsumed carbohydrates during the winter months. (R. Wurtman Tr. pp. 26-27; J. Wurtman pp. 164-65). Then, once they demonstrated that this overconsumption pattern did exist, they administered the serotonin-releasing agent fenfluramine to determine whether that agent was effective in treating SAD patients. In 1987, they published the results of their clinical trial, which showed that fenfluramine markedly decreased carbohydrate intake in those patients. (R. Wurtman Tr. p. 27; J. Wurtman Tr. pp. 165-66; DTX XG p. 330). Also in 1987, the Wurtmans were issued **U.S. Patent No. 4,649,161** ("the **'161 patent**") entitled "Method for Treating Depression with D-Fenfluramine." (DTX WZ).

In February 1986, the Wurtmans began to study PMS. (R. Wurtman Tr. p. 28; J. Wurtman Tr. p. 166; PTX 126 (PMS study protocol) p. WURT-000947). Following the same procedure they had established with CCO and SAD patients, the Wurtmans first studied the food intake of women suffering from PMS to determine whether there were differences in the amount and types of food they consumed as compared to women who did not suffer from PMS. There [*34] had been anecdotal reports that women with PMS craved sweet or salty carbohydrates during the luteal phase of the menstrual cycle. (R. Wurtman Tr. pp. 27-28; J. Wurtman Tr. pp. 163-64, 167). However, prior to the Wurtmans' work, no scientific study had measured carbohydrate craving in general in women with PMS. (R. Wurtman Tr. pp. 29-31; J. Wurtman Tr. p. 167; Miller Tr. pp. 499-500).

Next, the Wurtmans prepared a clinical trial protocol proposing: (1) to measure the amount and type of food that women with PMS consumed during the luteal phase and compare it with the amount and type of food consumed during the follicular phase, and (2) if there was a difference, to determine the effect of the serotoninergic agent fenfluramine on the mood changes and increased carbohydrate consumption of women suffering from PMS. (PTX 126 at WURT-000949). On February 11, 1986, the protocol was submitted to the MIT institutional review board, the committee responsible for authorizing such studies. (R. Wurtman Tr. pp. 28-29; J. Wurtman p. 169; PTX 126 p. WURT-000947). This protocol, however, did not include the serotoninergic agent fluoxetine.

The protocol was approved on April 1, 1986, and the clinical [*35] trial commenced shortly thereafter. (R. Wurtman Tr. p. 32; J. Wurtman Tr. p. 170; PTX 158). Potential patients were examined by a gynecologist and psychiatrist, who used well-established rating scales to

confirm a diagnosis of PMS or severe PMS. (R. Wurtman Tr. pp. 32-34; J. Wurtman Tr. pp. 170-71; PTX 126 p. WURT-000955-60). The results of the food intake portion of the study demonstrated that non-PMS women did not alter their caloric intake and did not show a preference for any particular type of food. In contrast, women with PMS had a higher caloric intake and a higher intake of carbohydrates during the luteal phase of their menstrual cycle as compared to control subjects. (R. Wurtman 34:19-35:21, 36:17-37:7; J. Wurtman 167:17-168:21; PTX 89 at WURT-000577). Contrary to what was generally believed prior to their study, PMS patients craved all types of carbohydrates, sweet and salty. (R. Wurtman Tr. pp. 35-36; PTX 89 p. WURT-000577).

Once the intake portion of the study was completed, in the summer of 1986, those patients suffering from PMS participated in the second part of the protocol, the administration of fenfluramine to treat PMS. (R. Wurtman Tr. p.37). At that time, there [*36] were no known effective agents for the treatment of PMS. No one had ever used fenfluramine to treat PMS before, and the Wurtmans did not know what to expect. (R. Wurtman Tr. p. 38; J. Wurtman Tr. p. 171; PTX 1, col. 1, 1. 62-col. 2, 1. 2). The results from the use of fenfluramine to treat PMS were very positive. (R. Wurtman Tr. pp. 38-40; J. Wurtman 171:23-172:25; PTX 131 at HAM 04592). The patients showed major improvement, not only in carbohydrate cravings, but also in their mood. For the first time "they had something that really made them feel better when they had PMS." (R. Wurtman Tr. p. 38).

In early 1987, having obtained excellent results using fenfluramine, the Wurtmans discussed the possibility of administering another agent that might generate responses similar to those of fenfluramine to some of the PMS subjects who had participated in the fenfluramine study. n5 Dr. Richard Wurtman came up with the idea of fluoxetine, a known serotonin-enhancing agent, having become familiar with the drug from his research and from his work as a consultant to Dr. Ray Fuller at Lilly, the inventor of fluoxetine. (R. Wurtman Tr. pp. 40-41; J. Wurtman Tr. pp. 173-74). At this time, several [*37] clinical researchers had access to fluoxetine and had published clinical trial results on its use in other disorders, which showed that fluoxetine was safe. (R. Wurtman pp. 42-43; 43-44; see DTX AC, GB). Dr. Wurtman testified that he requested a quantity of fluoxetine directly from Dr. Fuller, his friend of twenty years, as he had done previously approximately ten or fifteen times over the years. (Id. p. 94)

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n5 Teva challenges Dr. Richard Wurtman's memory on this point at his deposition, but we find his trial testimony, which was corroborated by Dr. Judith Wurtman, credible. (J. Wurtman Tr. p. 174). The Wurtmans' testimony required them to remember various events that happened approximately fifteen to seventeen years ago, events which resemble in large part other clinical trials in which they have participated over the years. Such a time lapse would allow for some slippage in their memories as they piece back together again the events at issue in this trial.

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Dr. Richard Wurtman did not, however, have [*38] enough fluoxetine for a full-blown clinical trial. Therefore, in about May 1987, he conducted a case study of the treatment of PMS using fluoxetine. (R. Wurtman Tr. p. 41). At trial, Dr. Wurtman testified that the fluoxetine came directly from Dr. Fuller and that he never asked Dr. Fuller for large amounts of the drug; Dr. Wurtman's deposition revealed that at the time of the case study, Dr. Wurtman's graduate student was also doing research with fluoxetine, but it was

expressly limited to use on animals. (Id. p. 92-93). Because Dr. Wurtman and his graduate student had made a formal request of Lilly for the fluoxetine used in the rat study, had complied with all of the conditions placed on that request, and through that compliance did not indicate that the fluoxetine was used to treat humans, we conclude that the fluoxetine likely came from Dr. Fuller to Dr. Wurtman, as one insider to the other. (See R. Wurtman Tr. pp. 90-94.)

Although Dr. Wurtman testified that he conceived of a protocol for his case study, which he showed to four n6 of his patients to inform them of the experimental value of the case study, he never filed a protocol with the institutional review board at [*39] MIT, and if such a protocol ever existed, it no longer exists. The patients did not sign informed consent forms. (R. Wurtman Tr. pp. 43, 78, 89; J. Wurtman Tr. p. 174). It is Dr. Wurtman's belief that a disclosure to MIT was not necessary because MIT was not involved in this case study and it took place off-campus, at his apartment/office. (R. Wurtman Tr. pp. 44, 77-78, 85). n7

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n6 At his deposition, Dr. Richard Wurtman testified that he gave fluoxetine to two women, not four. However, after reconstructing the different ways in which he tested the drug, Dr. Wurtman realized that his tests would have required four subjects, not two. (R. Wurtman Tr. pp. 82-84).

n7 With regard to Dr. Richard Wurtman's testimony that his case study was a "compassionate use," (R. Wurtman Tr. pp. 77-79, 106), we credit his understanding of the case study, but note that it likely would not have been the FDA's view of that use. Under a "compassionate use" exemption, a physician may apply to use a research drug, one not approved by the FDA, to treat a life-threatening condition where no alternative drug is available. (See **52 F.R. 19466 (1987)**; Miller Tr. pp. 248-49.) In May of 1987, the use of a non-FDA approved drug was only allowed to be under clinical investigation for "serious or immediately life-threatening disease condition" where no alternative drug or other therapy is available and where the drug is under investigation in a controlled clinical trial with an investigational new drug application filed with the FDA. (See **52 F.R. 19466 (1987)**.)

The parties did not argue what effect, if any, any alleged illegality as to Dr. Wurtman's actions would have on the validity of the '998 patent. The patent examiner was as aware of Dr. Wurtman's work as we are. Throughout the trial and in its briefs, Teva stresses the unlikelihood of Dr. Richard Wurtman's story of invention. However, while we noted that Dr. Wurtman's demeanor at trial was rather arrogant, as if the law had gotten in the way of the development of his research and the treatment of his patients, we did not find him to be untrustworthy. See also, supra, note 22.

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Dr. Richard Wurtman administered fluoxetine to one patient on a continuous basis every day of the month, during three menstrual cycles, and to the other three patients as reported in Example II of the '998 patent. (PTX 1; R. Wurtman Tr. pp. 44-45). To evaluate the effect of fluoxetine to treat PMS, the patients in the case study utilized the same PMS questionnaire that was used in the fenfluramine protocol. (Id. p. 44). Dr. Wurtman did not retain copies of those questionnaires. (Id. p. 90). Dr. Wurtman testified that the patients in the fluoxetine case study were "euphoric" over the beneficial effects of the fluoxetine and received the same improvement and relief from their PMS symptoms as was obtained using fenfluramine. (Id. p. 45). Dr. Judith Wurtman did not participate in the fluoxetine case study

(she is not a physician), and learned of the results only upon the filing of the '998 patent. (J. Wurtman Tr. pp. 174-75, 180-81.) In fact, no corroboration exists for Dr. Richard Wurtman's case study with one important exception, that is, the '998 patent.

After he analyzed the results of the fluoxetine case study, Dr. Richard Wurtman ultimately disclosed them to MIT, along [*41] with the results of the fenfluramine clinical trial, because he regarded them as an outgrowth of the fenfluramine clinical trial. (R. Wurtman Tr. p. 47). Together with the data from the fenfluramine clinical trial, the fluoxetine case study results formed the basis of the '998 patent application. (R. Wurtman Tr. pp. 45-47). As shown in the '998 patent, on average, women who took fenfluramine had more than a 50 percent reduction of symptoms based on their Hamilton Depression Scale ("HAMD") scores, and almost 100 percent reduction in their PMS Symptom Rating Scale scores. ('998 patent (PTX 1), col. 6, Tables 1-2). Likewise, patients who were treated with fluoxetine experienced a 75 percent improvement in mood ratings and a 70 percent improvement in appetite ratings, which results have been confirmed by other researchers. (R. Wurtman Tr. pp. 46-47; '998 patent (PTX 1), col. 6, ll. 50-59. See, e.g., PTX 60 pp. 1531-32; PTX 134 at Fig. 1, Fig. 2; PTX 40, Tables 1-4).

MIT authorized the filing of a patent application covering the Wurtmans' work. (R. Wurtman Tr. pp. 45, 47). On October 22, 1987, MIT filed U.S. Patent Application Ser. No. 111,771, naming Richard J. Wurtman and Judith [*42] J. Wurtman (collectively, "the Wurtmans") as inventors. On September 15, 1988, MIT filed U.S. Patent Application Ser. No. 244,944 as a continuation-in-part of Ser. No. 111,771. Although the patent at issue in this case, **U.S. Patent No. 4,971,998** ("the '998 patent"), issued from Ser. No. 244,944, the effective filing date of the '998 patent is October 22, 1987. During prosecution of the '998 patent, the patent examiner reviewed, among other things, patents and publications disclosing the use of fluoxetine to treat depressive and anxiety disorders and the use of fenfluramine to treat SAD and CCO, and publications discussing blood serotonin levels in PMS patients. The '998 patent, entitled "Methods For Treating the Premenstrual or Late Luteal Phase Syndrome," issued on November 20, 1990, to MIT as the assignee of the Wurtmans.

V. The State of the Art in 1987

A. The Nature of PMS

The '998 patent is directed to the use of fenfluramine and fluoxetine to treat PMS. Claim 2, the only claim at issue, states:A method for treating disturbances of mood, disturbances of appetite, or both, associated with pre-menstrual syndrome, comprising administering to a woman prior [*43] to the onset of her menstrual period, a composition consisting essentially of approximately 5 mg to approximately 120 mg of fluoxetine.('998 patent (PTX 1), col. 7, ll. 7-12.).

The Court has construed the claim terms "pre-menstrual syndrome," "disturbances of mood," "disturbances of appetite," and "prior to the onset of her menstrual period" as follows:1) the term "pre-menstrual syndrome" as used in Claim 2 of the '998 patent includes LLPDD/PMDD; 2) the term "disturbances of mood" we construe to mean negative changes in a person's normal mood associated with PMS; 3) the term "disturbances of appetite" we construe to mean negative changes to a person's normal appetite associated with PMS; and 4) "prior to the onset of her menstrual period" we construe to include not only late-luteal phase dosing regimens, but also all dosing regimens that begin prior to the onset of a woman's menstrual period, including those that go on continuously thereafter.(PTX 192 at 10, Dk # 119). n8 "PMDD" and "LLPDD" are terms that can be used interchangeably and refer to a severe type of PMS. (Rapkin Tr. pp. 601-02; Brown Tr. pp.

731-32).

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N8 A guide to the phases of a woman's menstrual cycle:

Women of child-bearing age experience monthly menstrual cycles, which prepare the body for a potential pregnancy. A woman's menstrual cycle begins on the first day of her period. Towards the beginning of the cycle, a hormone called follicle stimulating hormone ("FSH") is released from the brain. FSH stimulates the growth of 15 to 20 of the hundreds of thousands of immature eggs contained in a woman's ovaries. Each of the growing eggs is surrounded by a sac known as a follicle. As the follicles mature, they begin producing a hormone called estrogen, which stimulates the lining of the uterus, or endometrium, to thicken. One of the growing eggs will mature more quickly than the others and suppress the growth of the other eggs. (Miller Tr. pp. 210-11.)

At about midpoint in the cycle, a hormone called luteinizing hormone causes the dominant follicle to release its egg in a process called ovulation. After the egg is released, it enters the fallopian tube and journeys toward the uterus. If the egg is not fertilized, the endometrium begins to break down. The dead endometrial cells, along with blood and mucus, are discharged as menstrual flow. (Miller Tr. pp. 211-13.)

The menstrual cycle takes an average of 28 days. The follicular phase of the cycle begins with menstruation and ends with ovulation. Assuming a 28-day cycle, the follicular phase stretches from approximately day 1 to day 14. The luteal phase of the cycle begins with ovulation and ends with menstruation. Again, assuming a 28-day cycle, the luteal phase stretches from approximately day 14 to day 28 of the cycle. (Miller Tr. pp. 213-14.)

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Under the Court's definition, PMS includes PMDD and is a condition that begins during the luteal phase and remits during the follicular phase. (Endicott Tr. p. 1055; see also Smirz Tr. p. 1299). Teva's expert, Dr. Rapkin, confirmed at trial what she had written in 1987, that PMS was defined as "a cyclical disorder manifested by diverse physical and psychological symptoms in the luteal phase with relief soon after the onset of menses" and characterized by "a symptom-free week." (Rapkin Tr. pp. 588-90; DTX FF). Indeed, the "on-and-off nature" of PMS is an essential requirement of the disorder. (Endicott Tr. p. 1055; Smirz Tr. p. 1299). Therefore, a disorder related to PMS, premenstrual exacerbation, in which an underlying condition worsens during the luteal phase, would not, however, fall within the definition of PMS because there are no symptom-free days. (Endicott 1067:2-24, 1109:5-16; Smirz Tr. pp. 1303, 1305; Rapkin Tr. pp. 599-600, 601; see also Entry on Claim Construction pp. 6-7, 12 endeavoring not to broaden the claim term PMS beyond its plain meaning in 1987).

The Court construed the term PMS to be an "umbrella" term in that PMS can cover a number of different symptoms [*45] or complaints, and does not require that any specific symptom or complaint be present. (Endicott Tr. p. 1055; Smirz Tr. p. 1302). As construed by the Court, the term PMS encompasses over 150 different symptoms that are known to track in some women during the premenstrual phase. (Miller Tr. p. 215; Smirz Tr. p. 1302.) These symptoms can include both mood symptoms (e.g., depression, anxiety, or irritability) and physical symptoms (e.g., bloating, weight gain, and food cravings). (Smirz Tr. pp. 1302-03; Miller Tr. pp. 216-17; 226-27; R. Wurtman Tr. pp. 35-36, 56). Further

complicating a diagnosis of PMS is the fact that any one of its symptoms may occur in many different diagnostic contexts. (See Miller Tr. p. 254). The treatment of that symptom depends on the diagnostic context in which it occurs. (Endicott Tr. p. 1058; Smirz pp. 1303-04). PMS is not a subset of depression. (Rapkin Tr. pp. 607-608). What may be a symptom of PMS, e.g., depression or depressed mood, may also exist as a stand alone disease, e.g., major depression, which would require different treatment. (R. Wurtman Tr. p. 129-30.)

B. The Cause of PMS

As of October 1987, the etiology of PMS was unknown. (Miller [*46] Tr. pp. 455-56; Rapkin Tr. p. 623; Endicott Tr. pp. 1072-73). In 1985, David S. Janowky and Jeffrey Rausch published *Editorial: Biochemical hypotheses of premenstrual tension syndrome,"* 15 Psych. Med. 3-6 (1985) ("Janowsky"), in which they canvassed the knowledge landscape of PMS. Janowsky stated that researchers have tried to correlate changes in the menstrual cycle with changes in hormones (e.g., estrogen, progesterone, prolactin, mineralocorticoids and adrenocortical hormones), electrolytes, neurotransmitters (e.g., opioid polypeptides, cholinergic mechanisms, catecholamine alterations, and serotonin) and somatic parameters. (DTX CQ pp. 3-6; see also Endicott Tr. p. 1077; Smirz Tr. p. 1308.) Although Janowsky suggests that the same neurotransmitter thought to regulate affective disorders might modulate PMS, he admits that evidence of this connection is "by no means conclusive." (Id. p. 5). In November 1985, William R. Keye, Jr., stated, "Unfortunately, a survey of the medical and behavioral literature on premenstrual syndrome only points out the confusion surrounding this disorder." *Medical Treatment of Premenstrual Syndrome,* 30 Can. J. Psychiatry 483-87 (1985); [*47] (DTX CU p. 483). Even the '998 patent recognizes that as of its filing date there were multiple theories as to what caused PMS, and that none of those theories had been substantiated. (PTX 1, col. 1, ll. 37-61; R. Wurtman Tr. pp. 49-50). n9

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n9 Janowsky and Keye were not before the patent examiner, but as just described, they teach nothing that conflicts with the '998 patent.

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A leading theory in 1987 was one related to sex hormone changes (*i.e.,* progesterone) linked to a woman's menstrual period. (Endicott Tr. pp. 1077, 1153-54; Smirz Tr. p. 1307-08). Another, relatively new theory, was serotonin deficiency. Looking specifically at the hypothesis that a serotonin deficiency causes PMS, we determine what was known about that theory as of 1987. Serotonin was first suggested as a possible cause of PMS in 1979. (See, e.g., DTX GX). Reduced serotonin function was also known as of 1987 to result in symptoms of anxiety and depression. (See DTX A, WY). In addition, the Wurtmans own research demonstrated that [*48] serotonin regulated carbohydrate intake. (DTX WX).

As of October 1987, those skilled in the art were just beginning to discover the relationship between affective disorders and PMS. In 1985, Janowsky wrote that "[a] logical strategy for studying (premenstrual tension syndrome ("PMT")) may be to assume that the same neurotransmitter and neuromodulators thought to regulate affective disorders are those which also modulate PMT." (DTX CQ p. 5; see also DTX GX (March 1979) p. 361 ("Lowered levels of serotonin ... have consistently been associated with depressive states. Thus, one would predict depression just prior to menstruation, with some effect continuing for about a week.")). Also, in a November 1985 article, Renate DeJong, *et. al.,* stated that "the results of several studies suggest that a special relationship exists between premenstrual

syndromes and major psychiatric disorders, particularly affective illness." *Premenstrual Mood Disorder and Psychiatric Illness,* 142 Am. J. Psychiatry 1359 (1985). (DTX BC p. 1359). n10

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n10 In a study published in June 1987, Parry was motivated to test the effect of sleep deprivation, a known therapy for major depressive disorder, on PMS because "premenstrual syndrome and affective disorders may be related illnesses." (DTX DV p. 808). Although the Parry reference was not published more than a year before the effective date of the '998 patent and cannot be considered in our obviousness analysis, it is relevant in deciding the level of ordinary skill in the art.

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While PMS and affective disorders such as anxiety and depression share some common symptoms, they also have significant differences. For example, PMS is dependant on the menstrual cycle; thus, it, as a cyclic disorder, is characterized by symptom-free days. Depression, by contrast, involves an ongoing persistence of symptoms. (Rapkin Tr. pp. 588, 591-92; Blier Tr. pp. 1393-94, 1395). In 1987, it had not been proven that people suffering from PMS had the same biological characteristics as people suffering from depression. For example, PMS affects only women. (Rapkin Tr. pp. 604-05). PMS sufferers have some symptoms that patients with depression do not have (irritability and certain physical symptoms such as breast tenderness and bloating). Likewise, patients with depression have some symptoms that PMS sufferers do not have (depressed patients may experience early morning awakenings and evidence a lack interest in the world around them, and not all PMS patients are depressed). (Brown Tr. pp. 745-49). Because of these differences, a treatment designed for depression or anxiety would not necessarily be an effective PMS therapy.

Also in the early 1980s, clinical researchers attempted [*50] to measure the serotonin functioning in women with PMS to determine if a serotonin deficiency caused PMS. In a 1984 article, *Serotonin Levels and Platelet Uptake during Premenstrual Tension,* 12 Neuropyschobiology 16-18 (1984), Dorothy L. Taylor, *et al.,* studied the correlation between the severity of a woman's PMS and the decrease in that woman's peripheral serotonin levels. (DTX GP p. 16). She compared a woman's premenstrual platelet serotonin levels with her postmenstrual platelet serotonin levels, and the degree of change was correlated with the degrees of distress experienced by the patient pre-and post-menstrually. Building on Taylor's findings, in a study published in October 1987, n11 Andrea J. Rapkin, *et al.,* compared women with PMS to asymptomatic women and found changes in serotonergic function in patients with PMS. *Whole-Blood Serotonin in Premenstrual Syndrome,* 70 Obstetrics & Gynecology 533 (1987). (DTX FF pp. 536-37). Contrary to what is usually attributed to her, Rapkin did not find that PMS patients' serotonin levels decreased premenstrually. Rather, Rapkin showed that women with PMS had lower serotonin levels throughout the menstrual cycle, as compared [*51] with women who did not have PMS. (Blier Tr. pp. 1367-69; DTX FF at Fig. 1).

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n11 Although Rapkin's article does not qualify as **102(b)** prior art because it was not published more than one year before the filing of the '998 patent, this article was before the patent examiner.

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Dr. Blier, a serotonin expert testifying for Lilly, discounts Taylor's work because of "a major methodological flaw." Taylor only measured serotonin changes in women with PMS, and made no comparison of PMS patients with a control group of women who did not have PMS. (Blier Tr. pp. 1365-66; Endicott Tr. p. 1097). In addition, Dr. Blier challenges Rapkin's findings by showing that she did not control for diet, which was known in 1987 to affect serotonin. (Blier Tr. pp. 1369-70). Dr. Blier also argues that although blood platelets model serotonin neurons in the brain, changes in serotonin levels in the blood do not indicate the same type of activity in the brain, a fact Rapkin also noted in her article. (Blier Tr. pp. 1360-63; DTX FF p. 537; [*52] see also R. Wurtman Tr. pp. 59-61).

Although we credit Dr. Blier's testimony as to the mechanics of serotonin functioning and note his criticisms of the Taylor and Rapkin articles, we conclude that there is substantial evidence that those of ordinary skill in the art relied, at least in part, on Taylor and/or Rapkin, including the authors of the DSM-IV. (Miller Tr. pp. 319-20; see, e.g., DTX GG p. 242; WR p. 616;QQ p. SA 1520 1707; Endicott Tr. pp. 1189-94). These references, however, suggest only the involvement of serotonin with PMS, nothing more. (See Brown Tr. pp. 736-37; Endicott Tr. p. 1189). Neither doctor conducted a clinical trial of any drug, including fluoxetine. Furthermore, Rapkin specifically states that as of 1987 further studies were necessary "to elucidate the association between diminished peripheral serotonin and premenstrual syndrome."

C. The Treatment of PMS

Because the state of the art in 1987 was so uncertain and confused, doctors, n12 in an effort to treat patients presenting with PMS for the disorder as a whole, would nonetheless most likely have to target predominant or groups of symptoms for treatment. (See Endicott Tr. pp. 1155-56, 1158-59; [*53] Smirz Tr. pp. 1317-20, 28; Miller Tr. pp. 267-70). As of 1987, the only treatment that was believed to alleviate PMS as a syndrome would be directed at preventing ovulation, but that was not considered an acceptable treatment. (Endicott Tr. p. 1081; Miller Tr. p. 467; Smirz Tr. p. 1308). In a 1982 article entitled *The Premenstrual Syndrome: A Review of the Present Status of Therapy,* 24 Drugs 140-49 (1982), P.M.S. O'Brien (not an assumed name as we were informed) discusses the need for individualized assessments because of the wide variety of symptoms with which patients present. He then suggests that physicians treat their patients first with oral contraceptives or progestagen, and then, if neither of those options is effective, physicians should "determine the most distressing symptom or symptom type." (DTX DP pp. 147-48).

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n12 We find that these doctors, obstetricians, gynecologists, family physicians and psychiatrists, who regularly treat patients suffering from PMS qualify as those of ordinary skill in the art. They would be looking to solve a problem, so they would make themselves familiar with the relevant literature (Miller Tr. pp. 279-80), but they would be community-based (Endicott Tr. p. 1054). Physicians who conduct only clinical research on PMS, however, would be considered persons of more than ordinary, or extraordinary, skill in the art. (Brown Tr. pp. 761; Endicott Tr. p. 1054).

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As of 1987, a wide variety of drug therapies had been proposed for different groups of symptoms. If depression was the predominant symptom, the experts counseled caution. O'Brien found that, in general, "psychoactive drugs do not play an important role in treating the premenstrual syndrome." (DTX DP pp. 142, 148). As of the time of Keye's November 1985 article, "adequate trials of [MAO] inhibitors [and] of tricyclic antidepressant in premenstrual syndrome have not yet been reported. ... While psychoactive drugs may relieve a selected premenstrual symptom such as depression or anxiety, none would appear to be broad enough in its effect to provide satisfactory relief for women with severe and multiple symptoms." (DTX CU pp. 483-84). Furthermore, the relief available from the antidepressants available at the time, tricyclic antidepressants and MAO Inhbitiors, had to be weighed against their unpleasant side effects. (Miller Tr. pp. 267-68). For example, such risks and side effects include a risk of suicide with tricyclics (PTX 10 at 2627) and drug interactions with MAOIs (PTX 10 at 2563). ACOG did not recommend treatment of PMS with antidepressants until 1995. (Smirz Tr. pp. 1332.) [*55] Also, physicians were hesitant to prescribe antidepressants for treatment of PMS patients because of the perceived stigma associated with taking them. (Tollefson Tr. pp. 905-07; Smirz Tr. p. 1302).

Another treatment which was known to relieve, at least in part, the mood symptoms of PMS, but not the physical symptoms, was alprazolam, which is an anti-anxiety agent. However, alprazolam creates harmful side effects such as palpitations, tremors and seizures. (Miller Tr. pp. 465-66; Endicott Tr. pp. 1082-83). Additionally, physicians were not particularly comfortable using alprazolam to treat PMS in part because it is addictive. (Endicott Tr. pp. 1082-83).

Proponents of the serotonin hypothesis recommended testing agents that influence the serotoninergic pathway, namely tryptophan (DTX CQ p. 6; DTX FF p. 537) or chlorimipramine. (DTX CQ p. 6), or trazodone hydrochloride (DTX FF p. 537). Chlomipramine had been on the market since 1982. (Miller Tr. p. 461). As of October 1987, tryptophan had been shown to be an ineffective agent for treating PMS. In 1984, Dr. Endicott conducted a clinical trial using tryptophan and concluded it was totally ineffective in treating PMS. (Endicott Tr. pp. [*56] 1100-01; PTX 21 at 120). No one, however, had suggested the use of fluoxetine or fenfluramine, two known serotonin-enhancing agents. (Miller Tr. p. 404; Blier Tr. p. 1381-82; see also DTX WW (the '815 patent) at col. 3, ll. 34-35 (the described action of d,l-fenfluramine "appears to be mediated by the serotonergic system")).

With regard to fenfluramine, a non-psychotropic drug, Dr. Miller testified that it would be "highly unusual for a psychiatrist to use fenfluramine for any purpose." (Miller Tr. pp. 501-02). In addition, she is unaware of any OB/GYN who used fenfluramine to treat PMS prior to the Wurtmans. (Id. pp. 503-04.) In addition, Dr. Blier testified that the prior art teaches away from the use of fluoxetine to treat PMS. According to Rapkin's 1987 data, serotonin levels in whole blood were lower for women with PMS as compared to control subjects. Thus, one skilled in the art would want to increase whole blood serotonin levels. Fluoxetine, however, does the opposite; it decreases, not increases, whole blood serotonin. (Blier Tr. pp. 1381-82; PTX 52 at 14). Therefore, one skilled in the art who was relying on Rapkin's data would not have been motivated to use fluoxetine [*57] to treat PMS. (Blier Tr. pp. 1380-81, 1423-24).

As of October 1987, what was known about fluoxetine was that it was an effective treatment of depression and anxiety. Fluoxetine had been used in clinical trials since 1976, and studies confirming its efficacy in the treatment of major depressive disorder were published in 1985. (DTX AV, GB; Miller Tr. pp. 405-06). None of these prior art references, however, suggested the use of fluoxetine to treat PMS. Given the treatment options

described above, fluoxetine, with its high level of effectiveness and improved side effect profile, was a "therapeutic triumph." (Brown Tr. p. 774).

Although the Wurtmans were the first to propose fluoxetine as a PMS therapy in October 1987, Teva asserts that several other people arrived at the same conclusion at about the same time. On February 5, 1988, Wilma Harrison, et. al. ("the Harrison group"), proposed the *Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study.* (DTX OW). About five months later, on July 12, 1988, Andrea B. Stone and Dr. Brown, Teva's expert in this case ("the Stone group"), proposed an *Assessment of Fluoxetine in the Treatment of Premenstrual* [*58] *Syndrome.* (DTX NX; published as *Fluoxetine in the Treatment of Premenstrual Syndrome,* 26 Psychopharmacol. Bull. 331-35 (1990), DTX GJ). n13 As both of these studies were proposed after January 1, 1988, however, they likely reflect the subtle shift in the state of the art that occurred on that date when the FDA approved fluoxetine (Prozac) for the treatment of depression.

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n13 In July 1990, Karl Rickels, et al., published *Fluoxetine in the Treatment of Premenstrual Syndrome,* 48 Current Therapeutic Res. 161-66 (1990) ("Rickels"). (DTX FN.) As Rickels did not express interest in using fluoxetine to treat patients suffering from PMS until June 30, 1989, almost two years after the filing of the '998 patent, and did not publish his findings until July 13, 1990, we conclude that his contribution is too far removed to be considered probative of simultaneous invention. (See also D-Dem-H, listing physicians proposing the use of fluoxetine after 1989). By mid-1989, the Wurtmans and the Stone group were already speaking publically about and publishing their findings. (See J. Wurtman 185-87; DTX HM, XQ).

Teva also offers four letters to the editor offering anecdotal evidence of the use of fluoxetine to treat PMS prior to the issuance of the '998 patent. However, as stated at trial, these exhibits, DTX BQ, CO, DE and DY, are hearsay "plain and simple," and thus, not be considered evidence of simultaneous invention. See Tr. pp. 1181-82.

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Teva asserts that before FDA approval of fluoxetine, Lilly allowed its use only for research in furtherance of its commercial goals, which did not include an indication for PMS. Teva, however, does not support this allegation with evidence. In all of the voluminous exhibits that the parties have provided us, we see no letter dated before the filing of the '998 patent from a clinician to Lilly asking Lilly for fluoxetine with which to study the treatment of PMS or any letter from Lilly to any clinician denying him or her the same. In fact, when Drs. Stone and Brown proposed their study to Lilly in 1988, Lilly agreed to fund it even though Lilly indicated that it would not be seeking an indication for fluoxetine in the treatment of PMS. (See DTX XN, XO, XP, YB). n14

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n14 In 1992, after Lilly become aware of the '998 patent, when Drs. Brown and Stone applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Interneuron, then the exclusive licensee from MIT of the technology. (DTX OC, OD, OE).

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Although the subjects in the Harrison protocol had premenstrual exacerbation not PMS, the two study proposals offer, generally speaking, the same motivation to use fluoxetine to treat PMS: (1) patients with premenstrual depression have symptoms associated with affective disorders; (2) "pathophysiologic links between PMS and mood disorder" suggested that an agent like fluoxetine, which would lead to increased serotonergic activity may provide symptomatic relief from [PMS];" (3) fluoxetine had advantages over the then-existing antidepressants because it could address the increased appetite and sleep often found in patients with PMS; and (4) fluoxetine had a "relatively low incidence of troubling side effects" which would be "particularly suitable in treatment of women who are asymptomatic 75% of the time." (DTX XK; Brown Tr. pp. 666-71; see also DTX OX p. 2).

The scientific evidence that Dr. Harrison and Dr. Stone each relied on in deciding to use fluoxetine to treat PMS would have been available as of October 1987. (Brown Tr. pp. 680, 733-36.) However, the Harrison group and the Stone group would have viewed it differently from one of ordinary skill in the art. Each group, at [*61] the time it conducted is fluoxetine study, seriously considered other agents. After a review of the relevant literature, Dr. Stone's group decided against progesterone (Brown Tr. pp. 663-64), and the Harrison group was also conducting another study using nortriptyline to treat premenstrual depression (DTX FN p. 166). However, we conclude that the Harrison group and the Stone group would have been more likely to choose fluoxetine than another agent because one member of each group, Dr. Quitkin in the Harrison group and Dr. Brown in the Stone group, had participated in Lilly's clinical trials of fluoxetine to treat major depressive disorder, and thus would have been more familiar with the drug than would be one of ordinary skill in the art.

Dr. Brown testified that he had "more than a reasonable expectation" of success in using fluoxetine to treat PMS. (Brown Tr. pp. 820-21.) He explained, "That is why we did the study. Otherwise we wouldn't have done it." (Id. p. 821). Perhaps Dr. Brown's confidence was due to his superior knowledge of the efficacy of fluoxetine. Other clinical researchers, however, know that not all research will return the hoped for result (Endicott Tr. pp. 1101-02 describing [*62] the disappointing results of her tryptophan study), and do not profess such optimism in the results of their work at its outset. (R. Wurtman Tr. p. 38; J. Wurtman Tr. p. 171).

VI. Sarafem(R)

MIT, the original owner of the '998 patent, exclusively licensed the '998 patent to Interneuron on February 13, 1996. On June 19, 1997, Interneuron exclusively sub-licensed the '998 patent to Lilly. Armed with sufficient information about the safety and efficacy of fluoxetine in the treatment of PMS, Lilly finally decided to pursue commercial opportunities in that market. (See Tollefson Tr. p. 904.) Lilly offers this second license, which allegedly demonstrates the commercial value that it places on Sarafem, as objective evidence of the nonobviousness of the '998 patent.

Teva responds citing the testimony of its licensing expert, Mr. Gould. Mr. Gould testified that the 1997 license is not evidence of nonobviousness for two reasons, one of which we adopt. First, Mr. Gould opined that Lilly did not expect actually to have to pay running royalty rates in the amounts stated in the license (5% and 20%), an opinion with which Lilly's expert, Mr. Tate, disagrees. We need not determine [*63] the effective royalty rate for the '998 patent, however, because we agree with Mr. Gould's second point that the '998 patent would have had considerable value to Lilly regardless of its validity. n15

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n15 We do not intend to suggest that Lilly at any time thought the patent was invalid. Rather, we conclude only that the 1997 license is not objective evidence of nonobviousness. Substantial evidence exists that Lilly respected the validity of the '998 patent before licensing it, and that Lilly licensed it because Lilly believed it would be a commercial success. For example, in 1992, when Drs. Brown and Stone applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Interneuron, then the exclusive licensee from MIT of the technology. (DTX OC, OD, OE).

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Mr. Gould testified that, generally, there are two reasons a company may take a license: (1) for defensive purposes to prevent it from being sued as an infringer by the patentee; or (2) for offensive purposes [*64] to prevent others from entering the marketplace. (Gould Tr. pp. 1018-19.) Lilly could use the license offensively whether or not it believed the license to be valid. Once Lilly licensed the '998 patent, Lilly could list it in the Orange Book with respect to Sarafem. Lilly then would have standing to bring suit for infringement against a generic drug manufacturer and keep the generic manufacturer off the market for up to 30 months. The estimated sales value to Lilly of being the exclusive marketer of Sarafem was about $ 580,000,000. (Gould Tr. pp. 1018-23). Thus, we conclude that while the 1997 license had considerable value to Lilly, it is not evidence of nonobviousness.

Having licensed the '998 patent, on December 21, 1998, Lilly filed a Supplemental New Drug Application ("sNDA") with the U.S. Food and Drug Administration ("FDA") seeking approval to manufacture and market the use of fluoxetine to treat Premenstrual Dysphoric Disorder ("PMDD"). On July 6, 2000, Lilly received approval from the FDA to manufacture and market fluoxetine under the tradename Sarafem for treatment of Premenstrual Dysphoric Disorder ("PMDD"), a severe form of Premenstrual Syndrome ("PMS"). In August 2000, [*65] Lilly began marketing fluoxetine under the tradename Sarafem. (Dkt. 167).

From August 2000 through December 2002, sales of Sarafem in the United States totaled more than $ 176 million (Tate Tr. pp. 1216, 1222-23; PTX 156), and Sarafem was the market share leader for the treatment of PMDD. (Smith Tr. p. 951; PTX 120 at SA 1508 806). n16 However, Dr. Schmittlein, Teva's marketing expert, testified that Sarafem was not a commercially successful product "by Lilly's standards" because sales figures did not meet expectations. (Schmittlein Tr. pp. 1251-52, 1257; DTX RP p. SA 5 35). Dr. Schmittlein determined "Lilly's standards" from a speech made in 2002 by Jonathan Northrup, the Director of Strategic Asset Management for Lilly, in which he said that one of his primary responsibilities "over the past three years is really trying to exit the market from the $ 300 million type of product." (DTX SO at 24.)

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n16 The parties use data from August 2000 to December 2002, presumably the most recent figures available. Neither party introduced any evidence tending to show that this data is no longer representative of the market for Sarafem(R).

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Lilly is an international pharmaceutical company; its business strategies are not representative of what the broader pharmaceutical market would deem a commercial success. In fact, we find persuasive the patent certification letter that Teva sent to Lilly on February 19, 2002, which declared Sarafem to be a "commercially successful product" due in large part to the fact that "physicians felt comfortable prescribing Sarafem for PMS because of their familiarity with prescribing Prozac for depression." (PTX 98 at p. 9 or p. TEV-SA 06815; Schmittlein Tr. pp. 1285-86). Dr. Schmittlein also attempted to compare the sales of Sarafem to those of Prozac and Lipitor(R). (Schmittlein Tr. pp. 1254-57). Lipitor, the top-selling drug for 2002, lowers cholesterol; as Lipitor has nothing to do with PMS, we find its sales figures unhelpful. Dr. Schmittlein testified that Sarafem did not perform as well in its market (PMDD) as Prozac performed in its market (depression). However, because Prozac did extraordinarily well in its market, we don't find that to be a fair standard by which to evaluate Sarafem either.

Sarafem's prescription data supports a finding of commercial success. (PTX 120). Total prescriptions [*67] of Sarafem remained fairly constant, with only a slight decline, from 2001 to 2002. Repeat prescriptions of Sarafem, which Lilly's marketing expert Dr. Smith testified are highly indicative of the success of the inherent properties of the product, grew in 2002 compared to 2001 and remained stable through 2002, even though a competitor, Zoloft(R), was approved to treat PMDD in May 2002. (Smith Tr. p. 955-56; PTX 182 at SA 3542-44; PTX 120 at SA 1508 804). New prescriptions, which Dr. Schmittlein opined are the most important indicators of future product success, remained relatively stable from April 2001 (the first month after Lilly ended its direct-to-consumer marketing campaign) to April 2002 (the month before Zoloft was introduced). (Schmittlein Tr. pp. 1265-66). After the introduction of Zoloft to the market, the number of new Sarafem prescriptions declined slightly for the rest of 2002; however, Sarafem remained the market leader. (PTX 120 p. SA 1508 806).

Dr. Schmittlein opined that whatever success Sarafem did enjoy was attributable to Lilly's marketing efforts, and that in the absence of any marketing and advertising, the sales of Sarafem would drop to near zero by 2005. (DTX [*68] RV at SA 1508 809; Smith Tr. pp. 989-90; Schmittlein Tr. pp. 1267-69). Dr. Schmittlein offers many figures to describe how much money Lilly spent marketing Sarafem. (Schmittlein Tr. pp. 1259-63). For example, he asserts that approximately 80 percent of the $ 75.4 million Lilly spent developing Sarafem consisted of marketing expenditures. Again, however, Dr. Schmittlein does not identify a drug comparable to Sarafem so that we may understand these numbers in context. Considering that much of Sarafem's product development would have been coincident with the development of Prozac, spending 80 percent of development costs on marketing may not have been out of line. We also question the basis for the near zero sales figure (*i.e.*, what were the author's assumptions) and what would happen to the sales of a comparable drug in the absence of advertising.

In any case, as stated above, prescriptions of Sarafem remained relatively stable from 2001 to 2002, even though Lilly ended its direct-to-consumer marketing campaign in April 2001 and decreased its sales force from 1700 representatives in 2001 to 1020 in 2002. (DTX RV at SA 1508 818; Schmittlein Tr. p. 1261). Accordingly, we are convinced [*69] that Sarafem's commercial success derived from the merits of the drug rather than the marketing activities by Lilly.

VII. History of This Lawsuit

Lilly's sNDA for Sarafem contained a certification that the '998 patent covers the method of use of fluoxetine for which approval was being sought. Based on Lilly's certification, the FDA

listed the '998 patent in the FDA publication "Approved Drug Products with Therapeutic Equivalence Evaluation," commonly referred to as the "Orange Book," as covering Sarafem. On November 30, 2001, pursuant to **21 U.S.C. § 355(j)**, Teva filed an Abbreviated New Drug Application ("ANDA") seeking approval to engage in the commercial manufacture, use and sale of a generic version of Sarafem for the treatment of PMDD prior to the expiration of the '998 patent. Teva's ANDA included what is referred to as a "Paragraph IV" certification, which pursuant to **21 U.S.C. § 355(j)(2)(A)(vii)(IV)** stated that the '998 patent is "invalid, unenforceable, or not infringed by the manufacture, use or sale of Teva's fluoxetine [product]."

On April 5, 2002, Lilly sued Teva for infringement of the '998 patent. On June 17, 2003, Teva [*70] withdrew its patent misuse counterclaim. (Dk # 115). In view of our July 21, 2003 Entry on Claim Construction, on August 8, 2003, Teva stipulated to infringement of Claim 2 of the '998 patent under **35 U.S.C. § 271(b)** for purposes of trial. This stipulation was subject to Teva's right to appeal the Court's claim construction decision, the stipulation of infringement, and any consequent finding of infringement. On May 12, 2003, Magistrate Judge Shields issued an Entry Regarding Motion to Compel, which found that Lilly had not pled willful infringement in its Complaint. (Dk. # 96.) Lilly moved for reconsideration of the May 12, 2003 Order, or in the alternative, for leave to file an amended complaint. (Dk. # 105.) Teva opposed Lilly's motion and made a contingent motion to bifurcate the issue of willful infringement. (Dk. # 109, 110.) On November 3, 2003, the Court granted Lilly's contingent motion to amend its Complaint as well as Teva's contingent motion to bifurcate the issue of willful infringement. (Dk. # 182.)

Thus, the only remaining issues to be tried were Teva's invalidity defenses under **35 U.S.C. §§ 102** and **103**. The case was tried [*71] to the Court over a nine-day period between November 12 and November 24, 2003.

Conclusions of Law

The '998 patent is presumed to be valid under **35 U.S.C. § 282**. **Jones v. Hardy, 727 F.2d 1524, 1528 (Fed. Cir. 1984)**. Teva, the party challenging the validity of the '998 patent, bears the burden of proving invalidity by clear and convincing evidence. **Abbott Labs. v. Baxter Pharm. Prods., Inc., 334 F.3d 1274, 1282 (Fed. Cir. 2003)**. The Supreme Court has defined "clear and convincing" evidence as that which gives the finder of fact "an abiding conviction that the truth of [the proponent's] factual contentions are highly probable." **Colorado v. New Mexico, 467 U.S. 310, 316, 81 L. Ed. 2d 247, 104 S. Ct. 2433 (1983)**.

Where evidence of invalidity was before the patent examiner during prosecution, the challenger's burden is especially heavy; "he has the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with [*72] the level of skill in the art and whose duty it is to issue only valid patents." **McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1353 (Fed. Cir. 2001)** (internal citations omitted). However, where evidence concerning invalidity was not before the patent examiner during prosecution, no such deference is due with respect to evidence the examiner did not consider. **Structural Rubber Prods. Co. v. Park Rubber Co., 749 F.2d 707, 714 (Fed. Cir. 1984)**.

§ 102--Anticipation

Teva argues that the '998 patent is invalid as anticipated under **35 U.S.C. § 102(b)**. A

patent is invalid as anticipated if the claimed invention was "in public use or on sale in this country" or "described in a printed publication" at least one year before the effective filing date of the patent. In this case, the effective filing date of the '998 patent is October 22, 1987. A public use or prior art reference anticipates a patent claim if each and every limitation of that claim is found, either expressly or inherently, in that single public use or prior art reference. **Akamai Technologies, Inc. v. Cable & Wireless Internet Services, Inc., 344 F.3d 1186, 1192-93 (Fed. Cir. 2003)** [*73] (citing **Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1576-77 (Fed. Cir. 1991))**. "The dispositive question regarding anticipation is whether one skilled in the art would reasonably understand or infer from the prior art reference's teaching that every claim [limitation] was disclosed in that single reference." **Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1368 (Fed. Cir. 2003)** (internal quotation marks and alterations omitted).

Teva contends that Claim 2 of the '998 patent was inherently anticipated by one or all of the following prior art references: the '895 patent (DTX A), the **'213 patent** (DTX WY), the Stark article (DTX GB), and the Cohn article (DTX AV). In addition, Teva asserts that Lilly's Fluoxetine Trials are an inherently anticipating public use of the technology claimed by the '998 patent. "Newly discovered results of known processes directed to the same purpose are not patentable because such results are inherent." **Bristol-Myers Squibb Co. v. Ben Venue Lab., Inc., 246 F.3d 1368, 1377-78 (Fed. Cir. 2001)**.

Lilly, however, argues that Teva's cited prior art references and alleged [*74] public use do not anticipate Claim 2 of the '998 patent because they do not disclose the use of fluoxetine for "the same purpose." Rather, the prior art references and alleged public use direct the use of fluoxetine to treat affective disorders, a purpose different from the treatment of PMS. Because PMS is linked to the menstrual cycle, PMS is distinguishable from affective disorders, including depression and anxiety. For example, only women suffer from PMS, and their symptoms are on-again, off-again in nature, depending upon the menstrual cycle. As a result of these differences, a symptom common to both PMS and depression, such as depressed mood, may require different treatment depending on the context in which it appears.

Specifically, Lilly contends that to anticipate a claim reciting the use of an agent to treat a particular disorder, the prior art must disclose the use of that agent with the *intent* or *purpose* of treating the claimed disorder, here PMS. **Rapoport v. Dement, 254 F.3d 1053 (Fed. Cir. 2001)**; **Jansen v. Rexall Sundown, 342 F.3d 1329 (Fed. Cir. 2003)**. Teva, to the contrary, asserts that the authority relied upon by Lilly is factually [*75] distinguishable from this case.

The claim at issue in Jansen reads in pertinent part as follows:1. A method of *treating or preventing macrocytic-megaloblastic anemia* in humans which anemia is caused by ... which comprises administering a daily oral dosage of a vitamin preparation *to a human in need thereof* comprising ...**342 F.3d at 1330**. The Jansen court held that, as in Rapoport, "the claim preamble sets forth the objective of the method, and the body of the claim directs that the method be performed on someone 'in need.' In both cases, the claims' recitation of a patient or a human 'in need' gives life and meaning to the preambles' statement of purpose. ... The preamble is therefore not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of intentional purpose for which the method must be performed." **342 F.3d at 1333**.

To compare, Claim 2 states:A method for *treating* disturbances of mood, disturbances of appetite, or both, *associated with pre-menstrual syndrome,* comprising administering *to a*

woman prior to the onset of her menstrual period a composition [*76] consisting essentially of approximately 5 mg to 120 mg of fluoxetine."Teva argues that because Claim 2 "does not expressly limit treatment to individuals 'in need thereof,' the claim language 'a method for treating' should be construed as a 'statement of effect that may or may not be desired or appreciated.'" Teva Corrected Post-Trial Br. pp. 16-17.

Teva's argument, however, is incomplete. The Jansen court expressly declined to reach the situation we face here, one in which the "to a human in need thereof" phrase was not a part of the disputed claim. Jansen held only that the "to a human in need thereof" phrase *together with* the "treating or preventing" phrase required an intent to treat the specified condition. **342 F.3d at 1333**. Therefore, we must decide whether the "method for treating" phrase in the context of Claim 2 is sufficient to compel an intent to treat PMS.

Teva uses the prosecution history of **U.S. Patent No. 5,223,540** ("the '540 patent"), which issued from a later-filed application in the same chain as the '998 patent, to demonstrate the significance of the "human in need thereof" language. Teva contends that during prosecution, the patent [*77] examiner rejected a claim identical in form to Claim 2 of the '998 patent because the claim as written covered administration to "any woman." (DTX O p. 62). To address the examiner's concerns, the claim in the '540 application was amended to add the phrase "in need of such treatment." (DTX O pp. 75, 79). n17

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n17 The claim was amended as stated; however, we note that the examiner rejected the '540 amendment on obviousness grounds, a decision that was overruled on appeal. (DTX O p. 116).

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In response to Teva's argument, Lilly refers to a subsequent amendment to the '998 patent itself. The examiner initially rejected the amendment in part because the claims drew on an open host, *i.e.,* a woman, which could read on the same host as the prior art administration. However, in response to this rejection, the attorney prosecuting the patent argued that "the woman referred to in the cited claims is a woman in whom the mood and/or appetite disturbances described would otherwise occur prior to the onset of menstruation [*78] ... and possibly continue for several days ... after onset of menstruction." The examiner found the argument convincing and allowed the claim. (DTX N pp. 110, 116). Teva's expert, Dr. Miller, confirmed Lilly's interpretation of Claim 2 to require an intent to treat PMS when she testified that Claim 2 covers only women with PMS, as that term was defined by the Court. (Miller Tr. p. 383.)

Therefore, we conclude, as Lilly does, that Claim 2 requires an intent to treat PMS. In order to demonstrate an intent to treat PMS, Claim 2 uses the phrase "associated with PMS" to modify the "disturbance" being treated instead of the phrase "in need thereof" to modify "a woman," the subject of the treatment. As such, the phrase "associated with PMS" in the preamble is "not merely a statement of effect that may or may not be desired or appreciated. Rather, it is a statement of intentional purpose for which the method must be performed." See **Jansen, 342 F.3d at 1333**.

All the experts agree that Teva's alleged public use and prior art references--the '895 patent (DTX A), the **'213 patent** (DTX WY), the Stark article (DTX GB), the Cohn article (DTX AV), and the Lilly Fluoxetine Trials--do [*79] not include an intent to treat PMS. (Miller Tr. 429,

433-39 (regarding the **'895** and **'213 patent**s and the Stark and Cohn articles); Brown Tr. pp. 783-84 (regarding Stark article and clinical trials); Endicott Tr. pp. 1058-60, 1062 (regarding **'895** and **'213 patent**s and Stark and Cohn articles)). Accordingly, we find that Teva has failed to prove anticipation by clear and convincing evidence.

Although not necessary to our holding, we address Teva's additional arguments of anticipation in turn and find that they, too, are unconvincing. Teva's proposed prior art references, the '895 patent, the **'213 patent**, the Stark article, and the Cohn article, do not even suggest the claimed therapeutic use (to treat a diagnosed case of PMS). See **Merck & Co., Inc. v. Teva Pharms. USA, Inc., 347 F.3d 1367, 1372 (Fed. Cir. 2003)**. Nor do they limit the target of the treatment to women.

In addition, Teva cites Lilly's pre-October 22, 1986 Fluoxetine Trials as a public use inherently anticipating of each and every limitation of Claim 2. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. **MEHL/Biophile Intern. Corp. v. Milgraum, 192 F.3d 1362, 1365 (Fed. Cir. 1999)** [*80] (citing **In re King 801 F.2d 1324, 1326 (Fed. Cir. 1986))**. Recognition or appreciation of the newly-discovered necessary result by a person of ordinary skill in the art before the critical date is *not* required to show anticipation by inherency. **Schering Corp. v. Geneva Pharm., 339 F.3d 1373, 1377 (Fed. Cir. 2003)**.

Teva argues by analogy to an August 4, 1988 office action in which the patent examiner of the '998 patent rejected pending claims in part on the basis that the prior use of a drug (d-fenfluramine) in clinical work would have inherently anticipated the pending claims. Dr. Bolton, Teva's statistical expert, testified that, during open label clinical trials, Lilly or its agents administered fluoxetine in dosages between 5 mg and 120 mg to at least 112 women between the ages of 18 and 45 who had been diagnosed with major depressive disorder. Dr. Bolton stated that, based on a 65 percent prevalence rate of premenstrual depression among women with major depressive disorder, there was a greater than 99.9999% certainty that one or more of these 112 women was suffering from disturbances of mood associated with PMS when she participated in the [*81] clinical trial.

For a number of reasons, however, Dr. Bolton's analysis of the clinical trial evidence does not establish anticipation. First, the August 4, 1988 office action took place approximately 15 years before the Federal Circuit's decisions in Rapaport and Jansen, which we found applied to this case to require an intent to treat PMS. All the experts agree that the purpose of Lilly's Fluoxetine Trials was to determine the effectiveness of fluoxetine in the treatment of major depressive disorder, not PMS.

Second, Dr. Bolton's analysis is not based on a single prior art reference. **Structural Rubber Prod. v. Park Rubber, 749 F.2d 707, 715 (Fed. Cir. 1984)**; see also **Scripps Clinic & Research Foundation v. Genentech, 927 F.2d 1565, 1576-77 (Fed. Cir. 1991)** ("If it is necessary to reach beyond the boundaries of a single reference to provide missing disclosure of the claimed invention, the proper ground is not anticipation, but obviousness.") Rather, his calculations rely both on an examination of case report data and on 65 percent prevalence rate taken from the report of Teva's expert, Dr. Miller. (Bolton Tr. pp. 843, 851). Lilly challenges [*82] the accuracy of the prevalence rate chosen by Dr. Miller because it reflects the rate at which patients with major depressive disorder also had PMS at some point in their lifetime, not simultaneously with the disorder. See Lilly's Reply Br. p. 12. Teva responds that the calculations would remain relatively unchanged even if Dr. Bolton used a hypothetical prevalence rate of ten percent.

To the extent that Teva maintains that the prevalence rate is irrelevant, we agree, but for a

different reason. Dr. Bolton bases his testimony on probabilities--concededly, very strong probabilities, but probabilities nonetheless. A claim limitation is inherent in the prior art if it is necessarily present in the prior art, *not merely probably or possibly present.* **Rosco v. Mirror Lite, 304 F.3d 1373, 1380 (Fed. Cir. 2002)** (emphasis added). "Inherency ... may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, [*83] " the prior art has anticipated the claim at issue. **Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991)**.

Dr. Bolton's result is not a "necessary" or "natural" one. He could not identify any one patient record and say with certainty that any one female subject actually had PMS. **Contrast Proctor & Gamble Co. v. Nabisco Brands, Inc., 711 F. Supp. 759, 11 U.S.P.Q. 2d 1241, 1252-53 (D. Del. 1989)** (noting that defendant produced evidence that an employee of plaintiff produced the desired result following the claimed method on her first try). We find credible the experts' collective testimony that PMS requires a careful diagnosis, which to be confirmed must be charted over several menstrual cycles.

To supplement Dr. Bolton's statistical analysis, Teva offers the testimony of Dr. Brown to show that a patient record from Lilly's pre-October 1986 Fluoxetine Trials anticipated Claim 2. Dr. Brown testified that: (1) the subject woman suffered from disturbances of mood associated with PMS, and (2) both she and her physician appreciated that the fluoxetine she received in the clinical trial ameliorated those disturbances. This characterization [*84] misstates the facts, however.

In week 5 of the double-blind trial, the patient complained of "premenstrual tension," which abated as of week 6. Such an anecdotal comment is insufficient to diagnose PMS, however. Even Dr. Brown acknowledged that the patient was not given a thorough evaluation (*i.e.,* no documentation of the start of menses exists) and that frequently women erroneously attribute symptoms to PMS. Based on the structure of the clinical trial, we were able to determine that the patient was taking fluoxetine during the blinded portion of the trial. Depending on the length of the placebo lead-in period, by her fifth visit, she would have been taking fluoxetine for at least a week. Fluoxetine relieves symptoms of PMS within a day, but takes two to three weeks to relieve symptoms of depression. Therefore, we conclude that the patient did not suffer from disturbances of mood or disturbances of appetite associated with PMS.

The evidence as presented does not convincingly demonstrate a use of the method claimed in the '998 patent--the treatment of PMS. Nevertheless, Teva maintains that Lilly's Fluoxetine Trials constitute a "public use" under **§ 102**. The statutory phrase [*85] "public use" does not mean open and visible in the ordinary sense. Rather, it includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction, or obligation of secrecy to the inventor. **New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co., 298 F.3d 1290, 1297 (Fed. Cir. 2002)** (citations omitted). Because the inventors named on the '998 patent are Richard and Judith Wurtman, who were affiliated with MIT, and Lilly did not sublicense the '998 patent until 1997, almost a decade after the clinical trials at issue were completed, Teva contends that Lilly should therefore be considered a person other than the inventor who used the claimed invention.

We see at least two problems with Teva's contention. First, because Lilly's Fluoxetine Trials did not practice the claimed method, the use of fluoxetine to treat PMS, they do not constitute a "use" of the claimed invention, public or private. **Contrast SmithKline**

Beecham Corp. v. Apotex Corp., 365 F.3d 1306, 1318 (Fed. Cir. 2004) (concluding that where the claim covered the compound regardless of its use as an antidepressant, the clinical tests, which measured the [*86] efficacy and safety of the compound as an antidepressant, did not constitute an experimental use of the claimed invention, and thus that the use was public). In addition, unlike the clinical trial records in **SmithKline,** both Lilly and the Fluoxetine Trial investigators were required to maintain the confidentiality of their records. Therefore, during the prosecution of the '998 patent from 1987 to 1990, the Wurtmans and MIT would not have had access to the clinical trial records and could not have disclosed them to the patent examiner. In any event, we conclude the absence of the Fluoxetine Trial records is not material given the examiner's citations to the '895 and '213 patents. He would likely have been aware of Lilly's use of fluoxetine to treat depression during the prosecution of the '998 patent. (DTX M p. 253).

Because Teva has not demonstrated that the alleged prior art references require an intent to treat PMS (or even suggest such a therapeutic use), and because Teva has not established that Lilly's Fluoxetine Trials constitute a public use inherently anticipating each and every limitation of Claim 2, Teva has not proven by clear and convincing evidence that the '998 patent [*87] is anticipated under **§ 102**.

§ 103--Obviousness

A patent claim is invalid under **35 U.S.C. § 103(a)** "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." The ultimate determination of whether an invention would have been obvious under **§ 103(a)** is a legal conclusion based on underlying findings of fact. **Velander v. Garner, 348 F.3d 1359, 1363 (Fed. Cir. 2003)** (citing **In re Kotzab, 217 F.3d 1365, 1369 (Fed. Cir. 2000))**. The underlying factual inquiries include (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; and (3) the differences between the claimed invention and the prior art. **Id.** (citing **Graham v. John Deere Co., 383 U.S. 1, 17, 15 L. Ed. 2d 545, 86 S. Ct. 684 (1966))**. In addition, where offered, the court must also consider a fourth factor, objective indicia of nonobviousness. **Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1343 (Fed. Cir. 2000).** [*88]

If all the elements of an invention are found in a combination of prior art references, a proper analysis under **§ 103** requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they carry out the claimed process; and (2) whether the prior art would also have revealed that in so carrying it out, those of ordinary skill would have a reasonable expectation of success. **Velander, 348 F.3d at 1363** (citing **In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991)**, and **In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988))**. This reasonable expectation of success does not require a showing of "absolute predictability." **Yamanouchi, 231 F.3d at 1343**. Whether a motivation to combine prior art references has been demonstrated is a question of fact. **Winner International Royalty Corp. v. Wang, 202 F.3d 1340, 1348 (Fed. Cir. 2000)**. Both the motivation to combine references and the reasonable expectation of success must be founded in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be [*89] solved. **Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000)**. They may not, however, be taken from the applicant's disclosure." **Velander, 348 F.3d at 1363**.

A. Scope and content of prior art

The obviousness of a claimed invention under **§ 103** must be assessed as of the "date of invention." The date of invention is deemed to be the date on which the inventor filed its patent application, the "constructive reduction to practice," unless the inventor furnishes sufficient proof of an earlier "conception" and "actual reduction to practice." See **Kridl v. McCormick, 105 F.3d 1446, 1449-50 (Fed. Cir. 1997)**; see also **Brown v. Barbacid, 276 F.3d 1327, 1339 (Fed. Cir. 2002)**. "Conception is the formation in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is therefore to be applied in practice. Conception must include every feature or limitation of the claimed invention. **Kridl, 105 F.3d at 1449-50** (citations omitted). An actual reduction to practice requires a determination that the inventor's conception, [*90] including all its limitations, will work for its intended purpose. **Cooper v. Goldfarb, 154 F.3d 1321, 1327-28 (Fed. Cir. 1998)**.

"Conception must be proved by corroborating evidence which shows that the inventor disclosed to others his complete thought expressed in such clear terms as to enable those skilled in the art to make the invention." **Kridl, 105 F.3d at 1449-50** (citations omitted). Similarly, in order to establish an actual reduction to practice, an inventor's testimony must be corroborated by independent evidence. **Cooper, 154 F.3d at 1330**. The inventor's own statements and documents are not enough. **Hahn v. Wong, 892 F.2d 1028, 1032 (Fed. Cir. 1989)**.

In this case, the filing date of the '998 patent is October 22, 1987. The only evidence Lilly offers to support an earlier date of invention is the testimony of the inventor, Dr. Richard Wurtman. Lilly does not produce any document or witness testimony to corroborate his testimony. Dr. Judith Wurtman, a co-inventor, was not involved with the fluoxetine study; she did not see the results except as they were presented in the '998 patent. Therefore, in the absence [*91] of sufficient proof of an earlier conception and actual reduction to practice, we must conclude that the date of invention is the filing date of the '998 patent, October 22, 1987. Accordingly, the relevant prior art consists of those references dated one year or more before the date of invention. In this case, that date is October 22, 1986. See **Scripps Clinic & Research Foundation, 927 F.2d at 1576-77**.

Next, we must determine what the prior art had taught about fluoxetine as of the filing of the '998 patent. Although fluoxetine was not on the market in the United States, it was available in Europe as of November 1986. Clinical trials involving fluoxetine and the nature of the drug itself had also been described in the scientific literature.

In its obviousness argument, Teva again relies on the prior art discussed in our anticipation analysis, among other references. The '895 patent, which was filed in September 1975 and issued in April 1977, teaches that fluoxetine is an effective treatment of depression in humans. Similarly, the **'213 patent**, which was filed in 1983 and issued in 1986, establishes that fluoxetine is an effective treatment of anxiety in humans.
In [*92] separate articles in March 1985, Cohn and Stark tested the efficacy of fluoxetine and found that fluoxetine relieved the symptoms of depression significantly better than placebo and that it caused fewer and less severe side effects than another antidepressant, impramine. n18 These prior art references teach all but one, key element of the '998 patent--that fluoxetine is an effective treatment of symptoms *associated with PMS.*

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n18 Other publications of the same era support these findings. For example, in December 1986, Benfield *et al* published a drug evaluation, which stated that fluoxetine was known to

be a SSRI, and therefore, to be effective in treating conditions caused by serotonergic deficiencies, including depression. (Miller Tr. pp. 250-51; DTX AC pp. 482-83). Benfield also discussed fluoxetine's side effect profile, which improved upon that of tricyclic antidepressants. Id. p. 484. This reference was published after October 1986, but it was before the patent examiner during the prosecution of the '998 patent.

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In order to determine whether one of ordinary skill in the art would have thought it obvious to use fluoxetine to treat PMS, we must first establish what was known about PMS as of October 22, 1987. The answer is not much. There were many theories as to the cause of PMS, but none had been definitively proven. In 1985, after having surveyed the many theories as to the etiology of PMS, Janowsky stated that "no existing hypothesis of PMT [premenstrual tension syndrome] is even close to being proved at this time." (DTX CQ p. 7). While a leading theory in 1987 was one related to sex hormone changes (*i.e.,* progesterone) linked to a woman's menstrual period, many other theories were being tested. Another theory, which will be discussed below, was serotonin deficiency.

In considering whether one of ordinary skill in the art would have been motivated to use fluoxetine, an effective treatment of depression, to treat PMS, we note as of October 1987, the nature of the relationship between PMS and affective disorders was still being explored. PMS is not a subset of depression, which is itself a stand alone affective disorder. Depression in the sense of depressed mood, however, may be a symptom [*94] of PMS. There are significant differences between PMS and affective disorders such as depression or anxiety. PMS is dependant on the menstrual cycle; thus, it, as a cyclic disorder, is characterized by symptom-free days. Depression, by contrast, involves an ongoing persistence of symptoms. PMS affects only women whereas both men and women suffer from depression. PMS sufferers have some symptoms that patients with depression do not have (irritability and certain physical symptoms such as breast tenderness and bloating). Likewise, patients with depression have some symptoms that PMS sufferers do not have (depressed patients may awake early in the morning and lack interest in the world around them, and not all PMS patients are depressed). Because of these differences, a treatment designed for depression or anxiety would not necessarily be an effective PMS therapy.

As of October 1987, those skilled in the art were just beginning to look past these differences to discover the relationship between affective disorders and PMS. In February 1985, Janowsky suggested in a journal editorial that "[a] logical strategy for studying [premenstrual tension syndrome ("PMT")] may be to assume that [*95] the same neurotransmitter and neuromodulators thought to regulate affective disorders are those which also modulate PMT." (DTX CQ p. 5). See also DTX GX (March 1979) p. 361 ("Lowered levels of serotonin ... have consistently been associated with depressive states. Thus, one would predict depression just prior to menstruation, with some effect continuing for about a week."). Also, in a November 1985 journal article, DeJong, *et. al.,* stated that "the results of several studies suggest that a special relationship exists between premenstrual syndromes and major psychiatric disorders, particularly affective illness." (DTX BC p. 1359). n19

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n19 None of these prior art references were in front of the patent examiner during the prosecution of the '998 patent. However, the theories proposed by these references are very similar to the serotonin hypothesis Rapkin tested in her 1987 article, which was before the patent examiner.

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Also in the early 1980s, clinical researchers attempted to measure the serotonin functioning [*96] in women with PMS to determine if a serotonin deficiency caused PMS. In 1984, Taylor studied the correlation between the severity of a woman's PMS and the decrease in that woman's peripheral serotonin levels. Building on Taylor's findings, in a study published in October 1987, Rapkin compared women with PMS to asymptomatic women and found that women with PMS had lower serotonin levels throughout the menstrual cycle.

Lilly's expert witness, Dr. Blier, tried to discredit Taylor's study by arguing that she did not have a control group of asymptomatic women. In addition, Dr. Blier challenged Rapkin's findings by showing that (1) she did not control for diet, which was known in 1987 to affect serotonin, (2) blood serotonin levels of women with PMS did not change during the menstrual cycle, and (3) although blood platelets model serotonin neurons in the brain, changes in serotonin levels in the blood do not indicate the same type of activity in the brain.

Although we credit Dr. Blier's testimony as to the mechanics of serotonin functioning and note his criticisms of the Taylor and Rapkin articles, Drs. Taylor and Rapkin are not on trial here. Substantial evidence exists that those of ordinary [*97] skill in the art relied, at least in part, on Taylor and/or Rapkin, including the authors of the DSM-IV, who derived the definition of PMDD followed by the American Psychiatric Association. In determining obviousness, references are read not in isolation but for what they fairly teach in combination with the prior art as a whole. **In re Merck & Co., 800 F.2d 1091, 1097 (Fed. Cir. 1986)**. Together, these references support the involvement of serotonin with PMS, but it ends there. Neither doctor conducted a clinical trial of any drug, including fluoxetine. Furthermore, Rapkin specifically states that as of 1987 further studies were necessary "to elucidate the association between diminished peripheral serotonin and premenstrual syndrome." (DTX FF p. 537).

Although the serotonin hypothesis was gaining ground, it was still one theory among many. In Janowsky's 1985 article, he noted that researchers had tried to correlate changes in the menstrual cycle with changes in everything from hormones (e.g., estrogen, progesterone, prolactin, mineralocorticoids and adrenocortical hormones), to electrolytes, to neurotransmitters (e.g., opioid polypeptides, cholinergic mechanisms, to [*98] catecholamine alterations, and serotonin), to somatic parameters. (DTX CQ pp. 3-6).

Given the uncertainty surrounding the cause of PMS, we next determine how one of ordinary skill in the art would have approached treating the syndrome. The parties devoted much energy in their briefing to the extent to which PMS was treated symptomatically in 1987, too much in our view. Doctors treating a patient presenting with PMS would have been motivated to seek treatment for the disorder as a whole. However, because the etiology of PMS was and is not known, doctors would most likely have had to target predominant or groups of symptoms for treatment. In 1982, O'Brien discusses the need for individualized assessment because of the wide variety of symptoms with which patients present. He then suggests that physicians treat their patients first with oral contraceptives or progestagen, and then, if neither of those options is effective, physicians should "determine the most distressing symptom or symptom type." (DTX DP pp. 147-48).

If depression was the predominant symptom, the experts counseled caution. O'Brien found that, in general, "psychoactive drugs do not play an important role in treating [*99] the premenstrual syndrome." (DTX DP pp. 142, 148). As of Keye's November 1985 article, "adequate trials of [MAO] inhibitors [and] of tricyclic antidepressant in premenstrual syndrome have not yet been reported. ... While psychoactive drugs may relieve a selected premenstrual symptom such as depression or anxiety, none would appear to be broad enough in its effect to provide satisfactory relief for women with severe and multiple symptoms." (DTX CU pp. 483-84). Furthermore, the relief available from the antidepressants available at the time, tricyclic antidepressants and MAO Inhbitiors, had to be weighed against the unpleasant side effects. For example, such risks and side effects include risk of suicide with tricyclics (PTX 10 at 2627), drug interactions with MAOIs (PTX 10 at 2563), and lithium toxicity with lithium. ACOG did not recommend treatment of PMS with antidepressants until 1995.

Another treatment which was known to relieve, at least in part, the mood symptoms of PMS was alprazolam, which is an anti-anxiety agent. However, alprazolam has harmful side effects such as palpitations, tremors and seizures. Additionally, physicians were not particularly comfortable using alprazolam [*100] to treat PMS in part because it was addictive.

Proponents of the serotonin hypothesis recommended testing agents that influence the serotoninergic pathway, namely tryptophan, chlorimipramine, and trazodone hydrochloride. As of October 1987, however, tryptophan had been shown, by Dr. Endicott, to be ineffective agent for the treatment of PMS. Noticeably, no one suggested the use of fluoxetine or fenfluramine, two known serotoninergic enhancing agents, to treat PMS before the Wurtmans. Given the available treatment options, fluoxetine, with its high level of effectiveness and improved side effect profile, understandably was a "therapeutic triumph." (Brown Tr. p. 774).

B. Level of ordinary skill in the prior art

The parties dispute the appropriate level of ordinary skill in the art. Lilly argues that the one of ordinary skill in the art is a community-based OB/GYN or family practitioner. Teva, by contrast, contends that "the person of ordinary skill in the art must be an individual who, in the October 1987 time frame, would have been seeking to find a medication that would be effective in treating the specific PMS symptoms listed in claim 2 of the '998 patent-disturbances [*101] of mood and/or appetite." Teva Corrected Post-Trial Br. p. 24. The Federal Circuit teaches that factors pertinent to ascertaining the theoretical ordinary level of skill in the art are: (i) the inventor's educational background; (ii) the kinds of problems confronted in the art; (iii) solutions found previously; (iv) the speed of innovation in the art; (v) the level of sophistication of the technology; and (vi) the educational level of active workers in the field. **Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983)**.

In this case, the Wurtmans, who were the inventors of the '998 patent, were clinical researchers interested in using serotoninergic drugs to alleviate a constellation of symptoms associated with PMS. Dr. Richard Wurtman has an M.D. and Dr. Judith Wurtman has a Ph.D. in cell biology. As explicated above, in October 1987, although many theories existed as to the cause and treatment of PMS, none was generally accepted. During the prosecution of the '998 patent, the art, including the theory of serotonin deficiency, was continuously evolving. The "educational level of active workers in the field" varied. Those active in the development [*102] of new drug therapies, such as clinical researchers like the Wurtmans, read academic literature and conducted experimental clinical trials. However, community-

based physicians, whether OB/GYNs, family practice physicians or psychiatrists, ordinarily did not.

In this context, we conclude that a community-based physician would not be one of ordinary skill in the art because, as Dr. Endicott acknowledged, community-based physicians, on average, not only do not conduct independent research or seek patents, but they also do not read academic literature. If a person is not generally aware of the relevant prior art, he or she cannot be considered someone of ordinary skill in that art. Yet, to limit "one of ordinary skill in the art" to clinical researchers would be too restrictive. Therefore, in our view, one of ordinary skill in the art is a hypothetical medical doctor (an OB/GYN, a family practice physician, or a psychiatrist) who: (1) regularly sees and treats patients suffering from PMS, and (2) is familiar with the relevant prior art. See **Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc., 777 F. Supp. 330, 352 (D. Del. 1991)** (finding that where the patent was directed [*103] to the development of beta-blockers for the treatment of hypertension, "the person of ordinary skill in the art would be an individual with a PhD degree in organic chemistry, with an emphasis in medicinal chemistry ..., who would have some experience with the development of beta-blockers, and would be thoroughly familiar with the prior art which discusses the structure-activity relationships of the existing beta-blockers and have knowledge of the methodologies of drug development").

C. Differences between the claimed invention and the prior art

From the prior art, as of October 1987, one of ordinary skill would have known that: (1) fluoxetine is an effective treatment of anxiety and depression in humans; (2) fluoxetine is effective because it inhibits serotonin reuptake by the neuron, thereby preventing or lessening the serotonergic deficiencies that cause depression and anxiety; (3) although depressed mood is a symptom of PMS, PMS is a condition wholly distinct from depression; (4) the etiology of PMS is unknown; (5) numerous theories exist as to the cause of PMS, one of which suggests that PMS is related to serotoninergic functioning; and (6) there was not a drug [*104] therapy available to treat PMS as a whole. To learn all of this information, however, one would have to survey prior art references numbering well into the double digits. Even then, one would not find a single references suggesting the use of fluoxetine to treat PMS.

We are very wary of using hindsight as a blueprint of our obviousness analysis. n20 The Federal Circuit has made clear that "the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references." **Ecolochem, 227 F.3d 1361, 1371-72**. As stated above, such a suggestion to combine references may be founded in the prior art references themselves, the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. **Brown & Williamson, 229 F.3d at 1125**. We note, too, that although the number of references used is not determinative, "the requisite prior art suggestion to combine becomes less plausible when the necessary elements can only be found in a large number of references." 2 Chisum on Patents § 5.04[1][e][vi].

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n20 Teva encourages us to consider the Wurtmans' own prior art (the **'445**, '815 and '161 patents as well as DTX XI, a volume in the Annals of the New York Academy of Sciences edited by the Wurtmans and dated July 1987) as evidence of the obviousness of the '998 patent. This prior art suggests that serotonin regulates carbohydrate intake in patients with

either CCO or SAD. Teva argues that given this knowledge, one of ordinary skill in the art would have discovered that serotonin regulates disturbances of appetite associated with PMS. However, no one connected serotonin and carbohydrate regulation with PMS, or taught the use of fenfluramine or fluoxetine to treat PMS, before the Wurtmans. Teva's reasoning would use the Wurtmans' innovations against them and constitute just the kind of connect-the-dots hindsight analysis the Federal Circuit counsels against.

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There is no suggestion of combining references in the prior art. In 1987, the hypothesis that a serotonin deficiency caused PMS was barely acknowledged, and thus, not compelling. With regard to Rapkin's 1987 article, the Wurtmans would not likely have relied on it because it went to print in the same month as they filed the '998 patent. At most, the prior art references invited those of ordinary skill in the art to explore further the relationship of serotonin to PMS. See **Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 (Fed. Cir. 1986)**. There was no indication in the prior art, however, that an agent thought to affect serotonin was an effective treatment for PMS. Contrast **Richardson-Vicks, Inc. v. Upjohn Co., 122 F.3d 1476, 1484-85 (Fed. Cir. 1997)** ("The prior art combinations of an analgesic [other than that proposed in the patent at issue] and a decongestant in a single unit dosage were known to be particularly effective for treating sinus headaches..."). In fact, tryptophan, an agent thought to influence the serotoninergic pathway, was shown to be completely ineffective in the treatment of PMS. Moreover, the prior art demonstrated [*106] that anti-depressants as a class were an incomplete treatment of PMS.

Given that there was no known cause or treatment of PMS, the nature of the problem to be solved may have created a "can't hurt to try" attitude in the mind of those of ordinary skill in the art. See **Pro-Mold and Tool Co., Inc. v. Great Lakes Plastics, Inc., 75 F.3d 1568, 1573 (Fed. Cir. 1996)** ("Suggestion to combine references 'may also come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem.'") (citations omitted). Considering that the need for an effective treatment was so great, that the symptoms of PMS and depression were similar, that the serotonin hypothesis was slowly gaining recognition, and that the side effects of fluoxetine were known to be mild as compared to other anti-depressants and anti-anxiety agents on the market in October 1987, perhaps in hindsight it would have been "obvious to try" fluoxetine to treat PMS. "An 'obvious to try' situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure [*107] itself does not contain a sufficient teaching of how to obtain the desired result, or that the claimed result would be obtained if certain directions were pursued." **Gillette Co. v. S.C. Johnson, 919 F.2d 720, 725 (Fed. Cir. 1990)** (internal citations omitted). However, "obvious to try" is not the standard in a **§ 103** obviousness inquiry. **Ecolochem, 227 F.3d at 1374**. Teva must point to "the specific sources of the motivation to combine prior art references" in order to prevail on this theory. Id.

Our considered judgment is that Teva has not provided clear and convincing evidence of a motivation to combine references. History has shown that not even those with extraordinary skill in the art and unfettered access to fluoxetine, clinical researchers at Lilly, for example, were motivated to treat PMS with fluoxetine prior to the Wurtmans.

One of ordinary skill in the art must also have a reasonable expectation of success, which we find also lacking here. In 1987, scant information was known about the etiology of PMS.

Any new method of treatment that proved to be effective would have been unexpected, and like fluoxetine, a "therapeutic triumph." In [*108] sum, we conclude that Teva has failed to produce clear and convincing evidence that "a skilled artisan confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the matter claimed." **In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998)**.

D. Objective indicia of nonobviousness

Our primary finding of nonobviousness is buttressed by secondary indicia of nonobviousness. Objective evidence such as commercial success, failure of others, long-felt need, and unexpected results must be considered before a conclusion on obviousness is reached. **Minnesota Min. and Mfg. Co. v. Johnson & Johnson Orthopaedics, Inc., 976 F.2d 1559, 1573 (Fed. Cir. 1992)**. "Evidence of secondary considerations may often be the most probative and cogent evidence in the record." **Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983)**. Lilly offers many alleged objective indicia of nonobviousness for our consideration.

1. Commercial success

With regard to commercial success, Lilly, the patentee, bears the burden [*109] of proving a "nexus," or a legally and factually sufficient connection between the proven commercial success and the patented invention. **Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1392 (Fed. Cir. 1988)**. The Federal Circuit has held that "a presumption arises that the patented invention is commercially successful 'when a patentee can demonstrate commercial success, usually shown by significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent.'" **Ecolochem, 227 F.3d at 1377**. Once Lilly makes the requisite showing of nexus between commercial success and the patented invention, the burden shifts to Teva to prove that the commercial success was instead due to other factors extraneous to the patented invention. Id.

Lilly has satisfied its burden by offering evidence that Sarafem, its product covered by Claim 2 of the '998 patent, had sales of $ 176.2 million from August 2000 to December 2002 and was the most prescribed product for the treatment of severe PMS during that time. See **Tec Air, Inc. v. Denso Mfg. Mich., Inc., 192 F.3d 1353, 1361 (Fed. Cir. 1999)** [*110] (providing that sales figures coupled with market data provide stronger evidence of commercial success than sales figures alone). As evidence of its market share, Lilly also produced Sarafem's prescription data.

Even though a competitor, Zoloft, entered the PMDD market in May 2002, total prescriptions of Sarafem declined only slightly from 2001 to 2002. Repeat prescriptions, which Lilly's expert Dr. Smith testified are highly indicative of the success of the inherent properties of the product, grew in 2002 as compared to 2001 and remained stable with a slight decline through 2002. Teva's expert, Dr. Schmittlein, opined that new prescriptions, not repeat prescriptions, are the most important indicators of future product success because they demonstrate whether physicians view the product as continuing to play an important role in their treatment practice. However, new prescriptions, too, remained stable from April 2001 (the first month after Lilly ended its direct-to-consumer marketing campaign) to April 2002 (the month before Zoloft was introduced). Although Zoloft's appearance on the scene no doubt diverted some new prescriptions from Sarafem, Sarafem remained the market leader. [*111]

Teva disputes even the presumption that Sarafem achieved "significant sales in a relevant market." Teva argues that Sarafem was not a successful product "by Lilly's standards" because sales of Sarafem did not meet Lilly's projections. Teva also offers expert evidence that Sarafem sales in its market did not mirror the sales of Prozac in its market and that Lilly did not think it worthwhile to continue a "$ 300 million type of product" like Sarafem. We find Teva's arguments largely beside the point and unpersuasive. Sales of Prozac were by every measure extraordinary, which make them an unreliable benchmark for commercial success. In addition, that Lilly, an international pharmaceutical company, might seek to divest itself of a "$ 300 million product" more likely reflects that company's internal strategic goals rather than an indication that Sarafem would not be "a commercial success" for another, smaller company. See **Eli Lilly and Co. v. Zenith Goldline Pharmas., Inc., 2001 U.S. Dist. LEXIS 18361 (S.D. Ind. 2001)** ("if the patented drug were not a commercial success, generic manufacturers would have little interest in offering their own versions of the drug"). In fact, [*112] the patent certification letter that Teva sent Lilly on February 19, 2002, declared Sarafem to be a "commercially successful product" due in large part to the fact that "physicians felt comfortable prescribing Sarafem for PMS because of their familiarity with prescribing Prozac for depression." (PTX 98 at p. 9.)

Having demonstrated commercial success, Lilly shifts the burden to Teva to prove that the commercial success was due to factors extraneous to the patented invention. In addition, Teva contends that whatever success Sarafem did have was attributable to Lilly's marketing efforts, and that in the absence of any marketing and advertising, the sales of Sarafem would have dropped to near zero by 2005. **In re Huang, 100 F.3d 135, 140 (Fed. Cir. 1996)** (explaining that "success is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention--as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter"). Teva offers much data to describe Lilly's marketing expenditures for Sarafem. For example, Teva asserts that approximately 80 percent [*113] of Lilly's "development costs" consisted of marketing expenditures. Importantly, however, Teva does not identify a drug with comparable economic performance to Sarafem permitting us to understand these marketing expenditures in context. Considering that much of Sarafem's product development would have been coincident with the development of Prozac, spending 80 percent of development costs on marketing may not have been inappropriate. We also question the basis for the near-zero sales figure (*i.e.*, what were the author's assumptions) and the effect the absence of advertising would have had on the sales of a comparable drug. This evidence notwithstanding, prescriptions of Sarafem remained relatively stable from 2001 to 2002, even though Lilly ended its direct-to-consumer marketing campaign in April 2001 and decreased its sales force from 1700 representatives in 2001 to 1020 in 2002. From this we believe that Sarafem's commercial success derived from the merits of the drug rather than the marketing activities by Lilly.

As additional evidence of nonobviousness, Lilly offers evidence that on June 19, 1997, Lilly sublicensed the '998 patent from Interneuron (the "1997 License"). Teva [*114] contends that this sublicense is not an objective indicator of nonobviousness for at least two reasons: (1) Lilly did not expect actually to have to pay running royalty rates in the amounts stated in the license (5% and 20%), and (2) Lilly had an incentive to license the '998 patent even if Lilly believed it to be invalid. We need not sort out the intricacies of the parties' experts' calculations of an effective royalty rate, however, because we accept Teva's contention that Lilly would have had an incentive to license the '998 patent, regardless of its validity.

We emphasize that in our view the licenses are a neutral factor. Substantial evidence exists that Lilly respected the validity of the '998 patent before licensing it, and licensed it because Lilly believed the treatment of PMS with fluoxetine would be a commercial success. For

example, in 1992, when Drs. Stone and Brown applied to Lilly for permission to do a follow-up study of fluoxetine in the treatment of PMS, Lilly referred them to Interneuron, then the exclusive licensee from MIT of the technology. In addition, Dr. Tollefson, Vice-President with Eli Lilly Research Laboratories, testified that Lilly licensed the patent [*115] in 1997 because, convinced of the safety and efficacy of the use of fluoxetine to treat PMS, the company had decided to pursue commercial opportunities in that market.

Nonetheless, we find credible the testimony of Teva's expert, Mr. Gould, to the effect that, generally speaking, there are two reasons for a company to take a license: (1) for defensive purposes, to prevent it from being sued as an infringer by the patentee; or (2) for offensive purposes, to prevent others from entering the marketplace. Obviously, Lilly could use the license offensively whether or not it believed the license to be valid. Once Lilly licensed the '998 patent, Lilly could list it in the Orange Book with respect to Sarafem. Lilly then would have standing to bring suit for infringement against a generic drug manufacturer and keep the generic manufacturer off the market for up to 30 months. The estimated sales value to Lilly of being the exclusive marketer of Sarafem was about $ 580,000,000. (Gould Tr. pp. 1018-23). Thus, while the 1997 license had considerable value to Lilly, it is not necessarily evidence of nonobviousness.

Ultimately, we find that Sarafem was a commercial success and as such, this factor [*116] weighs in favor of nonobviousness.

2. Long-Felt Need / Failure of Others / Simultaneous Invention n21

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n21 Lilly encourages us to consider Teva's "copying" of Sarafem as secondary evidence of nonobviousness. However, because the very nature of a generic drug indicates that it is equivalent to the branded drug in certain significant respects, Teva's demonstration of equivalency of Sarafem to the extent required by the FDA is not an indication of the non-obviousness of the claimed invention.

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Lilly asserts that, as of October 1987, there was a widespread failure of others to develop a safe and effective treatment for patients suffering from PMS. As established above, many hypotheses existed as to the etiology of PMS, but no known treatments had been devised or developed that provided relief to both the physical and emotional symptoms of PMS. Fluoxetine was the first drug to provide relief for both kinds of symptoms, and the '998 patent was the first indication that fluoxetine was effective for PMS. Teva, [*117] by contrast, contends that the long-felt need that existed was simply for a serotoninergic drug with fewer side effects, and that the discovery of the fluoxetine molecule itself, in the form of Prozac, satisfied this need. Teva's contention, however, fails to account for the specific need to treat PMS. The identification of fluoxetine as an effective treatment of PMS did not occur until the '998 patent.

Next, Teva argues that others of ordinary skill in the art not only did not fail to develop the patented technology, but they also discovered it simultaneously with the Wurtmans. n22 Teva offers two clinical study protocols, Harrison, et al.'s *Treatment of Premenstrual Exacerbation of Chronic Mild Depression with Fluoxetine: A Pilot Study* dated February 5, 1988, and Stone, et al.'s *Assessment of Fluoxetine in the Treatment of Premenstrual Syndrome* dated July 12, 1988, to establish simultaneous invention. n23

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n22 Teva stresses the unlikelihood of Dr. Richard Wurtman's story of invention. We, however, find him credible. While we agree with Teva that Dr. Wurtman's version of events cannot establish an earlier date of invention than the filing of the '998 patent, Teva noticeably fails to identify any effect of the alleged surreptitiousness of Dr. Wurtman's actions on the validity of the '998 patent. The patent examiner was as aware of Dr. Wurtman's work as we are. See also, infra, note 7. [*118]

n23 As explained, infra, note 11, Teva's other evidence of simultaneous invention is either irrelevant because it is hearsay or is dated after the Wurtmans and the Stone group had publicized their findings of fluoxetine's efficacy in treating PMS. Therefore, we do not consider it.

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With respect to simultaneous invention, "evidence of independent development of a patented device is indicative of obviousness if the circumstances of the development are shown to be similar to the state of the art when the patent was filed." **Pratt & Whitney Canada, Inc. v. U.S., 17 Cl. Ct. 777, 787 (Cl. Ct. 1989)** (citing **Stewart-Warner Corp. v. Pontiac, 767 F.2d 1563, 1570 (Fed. Cir.1985))**. Before we discuss the specifics of Teva's prior art references, we note the subtle change in the state of the art that occurred after the filing of the '998 patent in October 1987 and before the conception of any of these references stemming from the fact that, in January 1988, the FDA approved fluoxetine (Prozac) for the treatment of depression.

Although Teva asserts that before the FDA approved [*119] fluoxetine Lilly allowed its use only for research in furtherance of its commercial goals, which did not include an indication for PMS, Teva does not support this allegation with any corroborative evidence. In all of the voluminous exhibits which the parties have introduced into evidence, we find no request dated before the filing of the '998 patent from a clinician to Lilly asking Lilly for fluoxetine to permit the study of the treatment of PMS, or any letter from Lilly to any clinician denying him or her the same. In fact, when Dr. Brown proposed his study to Lilly in 1988, Lilly agreed to fund it even though Lilly indicated that it would not be seeking an indication for fluoxetine in the treatment of PMS.

In addition, Teva argues that the motivation to treat PMS with fluoxetine was provided by the impending FDA approval of the drug. See **Richardson-Vicks, 122 F.3d at 1484**. In Richardson-Vicks, numerous prior art publications indicated that the FDA would likely approve dosages of the claimed drug, ibuprofen, in range of the claimed invention. The motivation to substitute ibuprofen for other analgesics in the prior art was particularly strong among ibuprofen manufacturers [*120] because it would allow them to strengthen the name brand recognition. Id. Here, however, there was no effective treatment of PMS for which to substitute fluoxetine, and the prior art references hailing the effectiveness of fluoxetine in treating depression didn't mention PMS. Therefore, we find no basis to hold that FDA approval impacted the filing of the '998 patent.

Next, we evaluate Teva's offerings of "contemporaneous development." The Federal Circuit has noted that simultaneous development may or may not be indicative of obviousness. **Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452,**

1460 (Fed. Cir. 1984). Evidence of contemporaneous development that occurs after the date of the patented invention, however, will almost never be probative of the ultimate conclusion of obviousness. See **Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1380 n. 4 (Fed. Cir. 1986)** (contemporaneous development more than a year after the filing date of patent is "of little probative value").

Approximately four months after the filing of the '998 patent, the Harrison group proposed the use of fluoxetine to treat the premenstrual [*121] exacerbation of chronic mild depression. About nine months after the filing of the '998 patent, the Stone group proposed a study of fluoxetine in the treatment of PMS. Because there is no symptom-free period, the Harrison group's protocol did not address PMS specifically, although its motivations for using fluoxetine were approximately the same as the Stone group's: patients with premenstrual depression had symptoms related to affective disorders, fluoxetine was known to increase serotoninergic function in the brain, fluoxetine had advantages over the then-existing antidepressants because it could address the increased appetite and sleep often found in patients with PMS, and fluoxetine had a low incidence of side effects, which is more appropriate for women who are asymptomatic 50-75% of the time.

These research clinicians, however, are persons of extraordinary skill in the art, and thus, their discoveries are irrelevant to a **§ 103** obviousness analysis. Although it appears that at least one member from each team met the criteria of one of ordinary skill in the art (*i.e.*, he or she was a physician who both treats patients and is familiar with the relevant literature), it is also [*122] true that these teams were comprised of research clinicians and that at least one member of each team participated in Lilly's clinical trials of fluoxetine to treat major depressive disorder. Therefore, both the Harrison group and the Stone group were much more familiar with fluoxetine specifically than one of ordinary skill in the art would have been. n24 While the evidence relied on by the researchers may have been available to the person of ordinary skill in the art as of 1987, he or she would not have weighed the possible treatment options with a eye on fluoxetine.

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n24 We do not mean to suggest that, at that time, anyone at Lilly suggested the use of fluoxetine to treat PMS. Such speculation on the part of Lilly's counsel is not supported by the evidence.

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Even if we were to consider this evidence, it supports only an "obvious to try" theory. Although Dr. Brown testified that "there was more than a reasonable expectation" of success that fluoxetine would be an effective treatment of PMS, Dr. Richard Wurtman [*123] testified that at the time he conducted his case study of fluoxetine, he did not know what to expect. In addition, other clinical researchers like Dr. Endicott undertook similar studies of other proposed PMS therapies and were met with disappointment. Finally, we note that the Stone group chose to study fluoxetine only after first considering progesterone. And, at about the same time as the Harrison group was conducting its fluoxetine study, it was also looking at the treatment of premenstrual depression with nortriptyline. Therefore, even those of extraordinary skill in the art had to hedge their bets.

Although we are not persuaded by Teva's assertions of simultaneous invention, even if we were to be, "the virtually simultaneous making of the same invention does not in itself

preclude patentability of that invention." **Environmental Designs, Ltd v. Union Oil Co. of Cal., 713 F.2d 693, 698 n. 7 (Fed. Cir. 1983)**. Assuming *arguendo* that Teva did establish a simultaneous invention, we conclude that it would merely counterbalance the other secondary indicia of nonobviousness (commercial success, failure of others, long-felt need and unexpected results). It would not [*124] outweigh our primary finding that, in 1987, the technology claimed in the '998 patent would not have been obvious to one of ordinary skill in the art.

Conclusion

For the reasons explained above, we hold that Teva has failed to prove by clear and convincing evidence that the '998 patent was invalid as anticipated under **35 U.S.C. § 102** or as obvious under **35 U.S.C. § 103**. Accordingly, the '998 patent is valid and enforceable. n25

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n25 The only remaining issue still before the court is Lilly's claim of willful infringement.

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It is so ORDERED this 29 day of July 2004.

SARAH EVANS BARKER, JUDGE

United States District Court

Southern District of Indiana